FETAL DYNAMICS AND MATERNAL SMOKING

Application of new ultrasonic methods

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Abstract The primary aim of the study was to investigate fetal dynamics after cigarette smoking by women in the last trimester of normal gestation. For this purpose, a new phase-locking, echo-tracking system connected to a real-time ultrasound scanner was used for continuous measurement of pulses in the fetal descending aorta. An initial characterization of the physiological dynamic behaviour of this vessel showed that during the third trimester the apparent diastolic diameter increased, whereas the mean amplitude of the pulses remained constant, inferring an increase of the pulsatile increment of the transverse vessel area. Prolongation, within the physiological range, of the previous beat interval decreased the diastolic diameter and enhanced the pulse amplitude. The duration of the incremental phase of the pulse diminished with increasing distance from the heart and with decreasing duration of the previous beat interval. The pulse wave velocity increased with gestational age. - After maternal smoking of one cigarette the rate of fetal breathing movements increased, the short-term variability of the breath-to-breath intervals diminished, a clustering of the fetal breathing movements and gross movements occurred, the fetal heart rate increased, and the short-term beat interval variability decreased. In the diameter pulse, smoking increased the velocity of the ascending slope, the pulse amplitude and the apparent diastolic diameter, whereas the velocity of the descending slope decreased. The post-smoking fetal blood flow, as measured by a combination of real-time ultrasonography and pulsed Doppler technique, was enhanced in the descending aorta and the umbilical vein. The observed changes, including a suggestive increase in contractility of the fetal heart, in systemic blood pressure and placental blood flow, are compatible with a hypothetical, nicotine-induced activation of the fetal adrenergic system. The new techniques employed in the study demonstrate their applicability in testing physiological and pathophysiological responses of drugs in obstetrical practice.

Key words
Maternal smoking; Fetal breathing movements; Fetal movements; Fetal heart rate; Fetal aorta; Umbilical vein; Pulse waves; Blood flow; Ultrasound; Nicotine conc; Carboxyhemoglobin

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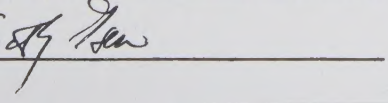
Signature 

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FETAL DYNAMICS AND MATERNAL SMOKING
Application of new ultrasonic methods

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ABBREVIATIONS

CTG: Cardiotocography = Registration of the fetal heart rate and the uterine contractions

CO: Carbon monoxide

Crest time: The time (in msec) from the onset of the pulse wave to its peak

ECG: Electrocardiogram

EEG: Electroencephalogram

FBM: Fetal breathing movements

FHR: Fetal heart rate

FM: Fetal body and/or limb movement

Inclination time: The length on the time axis (in msec) of a tangent to the steep ascending leg of the pulse curve, between the intercepts with the base level and the peak level, respectively

LDV: Late decremental velocity. The slope of the last part of the descending leg of the pulse curve (in mm/sec)

MIV: Maximum increment velocity. The maximum slope of the ascending leg of the pulse curve (in mm/sec)

PEP: Pre-ejection period. The time from the onset of the Q-wave in the fetal ECG to the opening of the aortic valve

Propagation time: The time (in msec) from the onset of the Q-wave in the fetal ECG to the foot of the pulse wave.

REM: Rapid eye movement

SDID: Standard deviation of the interval differences of consecutive heart beats (30 sec sample size); a measure of the short-term variability

TD-recorder: Time distance recorder

This thesis is based on the following original publications which will be referred to by their roman numerals.

I. Sindberg Eriksen P, Gennser G, Lindström K, Dahl P, Benthin M: Pulse wave recording - Development of a method for investigating fetal circulation in utero. J Med Engng Tech. Submitted.

II. Sindberg Eriksen P, Gennser G, Lindström K: Physiological characteristics of diameter pulses in the fetal descending aorta. Acta Obstet Gynecol Scand 63:355, 1984.

III. Sindberg Eriksen P, Gennser G, Löfgren O, Nilsson K: Acute effects of maternal smoking on fetal breathing and movements. Obstet Gynecol 61:367, 1983.

IV. Sindberg Eriksen P, Gennser G, Lindvall R, Nilsson K: Acute effects of maternal smoking on fetal heart beat intervals. Acta Obstet Gynecol Scand 63:385, 1984.

V. Sindberg Eriksen P, Gennser G: Acute responses to maternal smoking of the pulsatile movements in the fetal aorta. Acta Obstet Gynecol Scand. In press, 1984.

VI. Sindberg Eriksen P, Maršál K: Acute effects of maternal smoking on fetal blood flow. Acta Obstet Gynecol Scand. In press, 1984.

INTRODUCTION

Acute responses to smoking in adults

Habitual smoking among pregnant women is still common in spite of anti-tobacco campaigns (US Public Health Service, 1979). Cigarette smoking has several well-known effects on human physiological systems. In the central nervous system the cortical electro-encephalogram (EEG) has been found to change in response to smoking (Ulett & Itil 1969). When smokers are deprived of tobacco for a period of time, they spend more time in REM sleep than they would in the non-deprived state (Kales et al 1970). In adults, smoking produces a transient increase in breathing rate (Heymans et al 1931), heart rate, cardiac output and arterial blood pressure (Timisjärvi et al 1980) as well as an increased myocardial contractile force, a decreased pre-ejection period and an increased venous return (Rabinowitz et al 1979, US Public Health Service 1979).

Ultrasonic methods and variables for monitoring of fetal behaviour

The methods hitherto available for exploring the physiology of the cardiovascular and pulmonary systems have to a great extent been based on invasive techniques and are therefore not applicable to the human fetus <u>in utero</u>. Most of our present knowledge of fetal physiology is based on experiments with animal fetuses, using different kinds of invasive methods (Dawes 1968, Rudolph 1976). However, the introduction of ultrasound technique into perinatal medicine has promoted an almost explosive advance in our knowledge of the anatomy and physiology of the human fetus. After beginning with descriptive measurements of different parts of the fetal body, dynamic methods are now available for studying the behavioural functions of the undisturbed fetus. Real-time ultrasonography makes possib-

le the detection and recording of several fetal manifestations: hiccups, swallowing and changes in stomach volume, micturition, and eye movements (Maršál 1983). These latter activities, together with gross fetal movements and fetal heart rate (FHR), are regarded as indications of the fetal behavioural state. Ultrasound technique has become the method of choice for dynamic studies on fetal breathing movements (FBM) (Maršál et al 1978), the rate and variability of the fetal heart (Hammacher et al 1968), and the velocity of the blood flow (Eik-Nes et al 1980, 1983). Recently, with the introduction of a new phase-locking ultrasound system for the measurement of vessel pulsations, it has become possible to monitor the reactivity of the major fetal vessel in utero (Hokanson et al 1972, Korba et al 1979, Gennser et al 1981).

The first graphic records of FBM were presented by Ahlfeld in 1888. FBM are considered to represent a physiological phenomenon during the greater part of fetal life (Dawes 1973). Fetal respiratory movements (FBM) in the human fetus have been studied by the Time-Distance (TD) recording system connected to a real-time scanner (Maršál et al 1976, Lindström et al 1977) and the recording of FBM has been suggested for surveillance of high-risk pregnancies (Platt et al 1978, Trudinger et al 1979).

Fetal and intervillous blood flow are both important factors in maintaining intra-uterine life. Of particular interest is the flow through the fetal aorta and the umbilical vein, since the placenta, which serves the function of gas exchanger and energy supplier, is the organ which receives most of the flow in the fetal-placental unit (Rudolph 1976). The innovation of real-time ultrasound combined with pulsed Doppler technique has made possible the measurement of the blood flow in the fetal central vessels (Gill 1978, Eik-Nes et al 1980). An interdependence between FBM and blood flow has been

demonstrated, as FBM has been found to alter the blood flow pattern in the umbilical vein, the fetal descending aorta, and the fetal inferior vena cava (Maršál et al 1983). However, the possible role of breathing movements in the regulation of fetal blood circulation has not yet been evaluated. Propagation velocity and the contour of the pulse waves are important variables for analysis of the behaviour of the arterial tree and the ultimate wave shape is governed by a number of factors. The systolic acceleration slope is an accepted measure of the cardiac contraction force, while the steepness of the deceleration slope is a compound function of vessel wall compliance and peripheral resistance (McDonald 1974).

Acute fetal responses to smoking

In the human fetus the chronic effects of maternal smoking are most often described and an increased risk of premature birth, growth retardation and perinatal death has been found (US Public Health Service 1979). The acute responses to smoking are less completely known. In view of the general use of tests for perinatal supervision of the offspring, the immediate responses of the fetus to maternal smoking are of great clinical interest. Moreover, a closer analysis of the immediate responses of various fetal systems to maternal smoking might afford a better understanding of the observed smoking-induced effects resulting in the birth of a growth-retarded infant. Recording of the FHR has revealed a transient increase in the basal heart rate (Sontag & Wallace 1935, Doerfel 1952, Quigley et al 1979). Cigarette smoking has also been found to cause an immediate decrease in the intervillous placental blood flow (Lehtovirta & Forss 1978) and to depress both the differential index and the interval index, indices for both short-term and long-term variability of the fetal heart rate (Lehtovirta et al 1983, Rauramo et al 1983). In pregnant women, the smoking of one cigarette has

been found to cause a transient mild rise in baseline fetal heart rate, though no significant change was found in fetal heart rate reactivity (Barrett et al 1981), which indicates that the immediate effects of smoking a single cigarette are not responsible for the increased incidence of non-reactive non-stress tests in smokers (Phelan 1980).

Nicotine administration causes a sympathomimetic response due to the stimulation of sympathetic ganglia, activation of aortic and carotid body chemoreceptors and possibly, as a result, direct central stimulation of sympathetic tone (Armitage 1965). In animal studies, administration of large doses of nicotine to the pregnant rhesus monkey (Suzuki et al 1980) has been found to produce a significant, 38% reduction in the uterine blood flow, with concomitant acidemia and hypoxemia in the fetus. In humans, however, it is still an open question whether maternal smoking of a single cigarette will elicit the acute hypoxic response in the fetus, or whether the altered activity in the cardiovascular system found after smoking is solely or partly an expression of a sympathetic reaction to the smoking, as found in adults (Quigley et al 1979). Monitoring of the fetal vital systems by the use of various non-invasive methods under standardized conditions might therefore help to elucidate the nature and the extent of the fetal response to maternal smoking. Furthermore, this may yield an increased understanding of the physiology and pathophysiology of the human fetus <u>in utero</u>.

PURPOSES OF THE INVESTIGATION

The purpose of the present study was to investigate the immediate effects of maternal smoking on the fetal vital systems. For certain aspects of this study a newly developed phase-locking ultrasound system was used. The first part of the study concerned the testing and defining of the usefulness of a newly developed phase-locking ultrasound method for monitoring diameter changes. The second part evaluated the acute effects of smoking on the fetus using already established methods for exploring human fetal physiology and by using a phase-locking ultrasonic system.

The aims of part one were:

1. to test the capacity, accuracy, and the precision of a newly developed phase-locking echo-tracking ultrasound system designed for monitoring diameter pulsations in the major vessels of the human fetus to and evaluate its clinical applications;

2. to record and quantitate certain physiological characteristics of the pulsatile movements in the descending aorta of the human fetus in the last trimester of gestation.

The aims of part two were:

3. to record and quantitate some acute effects of maternal smoking on the breathing movements and gross movements of the fetus;

4. to record and quantitate certain immediate responses to maternal smoking evident in the fetal heart beat intervals;

5. to record and quantitate certain immediate responses to maternal smoking evident in the circulatory dynamics in the fetal descending aorta and the umbilical vein.

METHODS

Recording of diameter pulsations in the fetal vessels

The system used in the present study was specially designed for the non-invasive measurement of diameter pulsations in the fetal vessels (paper I). The starting point was the TD recorder which was constructed to measure FBM (Maršál et al 1976), based upon an electronic processing of signals obtained with a conventional real-time B-mode scanner with a linear array transducer which allows continuous recording of the movements of arterial walls. The principle of this system for measuring FBM includes the possibility of choosing any of the image lines of the real-time B-mode scanner and then to perform on-line measurements of the instantaneous distance between two selected, range-gated echoes along this line. Blood vessels, however, are to a large extent embedded in tissue whose acoustic impedance differs only slightly from that of the proper vessel walls. A different gating principle was therefore necessary to specifically detect the moving echoes of the vessel walls *in situ*. The amplitude-dependent range-gating echo-tracker in the TD recorder was replaced by a phase-locked loop device, as originally described by Hokanson et al (1972) and elaborated by Korba et al (1979). A gating pulse is used to select the desired cycle of the echo signal. The system detects the movement of the chosen echo by determining the phase shift that occurs relative to an electronic gate made as long as a whole wavelength, in order to facilitate the tracking of quick movements. When the moving echo is dislocated in the gate, a phase-locked loop replaces the gate pulse relative to the echo and the replacing steps of the gate are representative of the echo movement being sought. By doubling the phase-locking system it was possible to track two separate echoes simultaneously. Phase-locked tracking is virtually independent of the echo amplitude because the

phase shift is determined from the zero-crossing time. The echo-tracker being used combined with a real-time ultrasound scanner (ADR, Tempe, Arizona) with a 3.0 MHz linear array transducer, has a spatial resolution (50 μm) for detecting movements that far exceeds the ability of the scanner to distinguish stationary objects. The system was provided with a double phase-locking circuit in order to obtain differential measurements between the two output signals. A remote-controlled selector chooses the position of two horizontal marker lines indicating the tracking of each vessel wall along a selected image line. The distance between the two marker lines is selectively illuminated, which facilitates the operation by yielding a continuous supervision of the site of measurement and the quality of

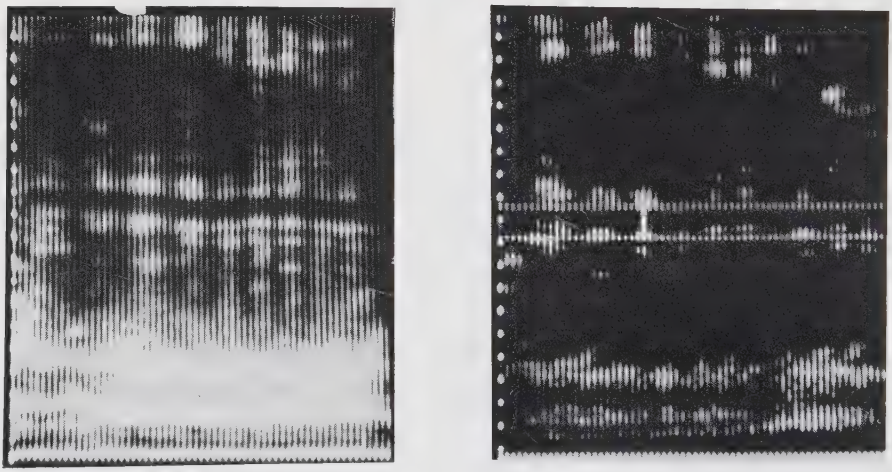

Fig. 1. (Left) Ultrasonic image of a segment of the descending aorta in a fetus at 36 weeks of gestation. (Right) The same image including the echo-tracking function. The two horizontal marker lines for tracking the aortic walls and the intensified vertical line representing the instantaneous vessel diameter are shown.

the insonation (Fig. 1). The line computer can excite the crystals of the ultrasound transducer in any order determined by a programmable scanning unit. This method allows the selection of crystals in two frames or more, before the same sequence reappears. This scanning order provides the production of a scanner image with a 40 Hz frame frequency combined with echotracking of a 2.56 kHz (or 1.28 kHz) repetition frequency at 10 cm (or 20 cm) depth. For monitoring of the pulsatile movements of the descending aorta, the vessel perpendicular to the beam is identified in a longitudinal ultrasound section of the fetus. Each of the two electronic markers of the tracking gate is digitally positioned over the echo image of each vessel wall. The distance between them is then measured automatically in a plane perpendicular to the longitudinal axis of the vessel. The output signal (Fig. 2) represents the instantaneous change in the vessel diameter calibrated absolutely in time and amplitude.

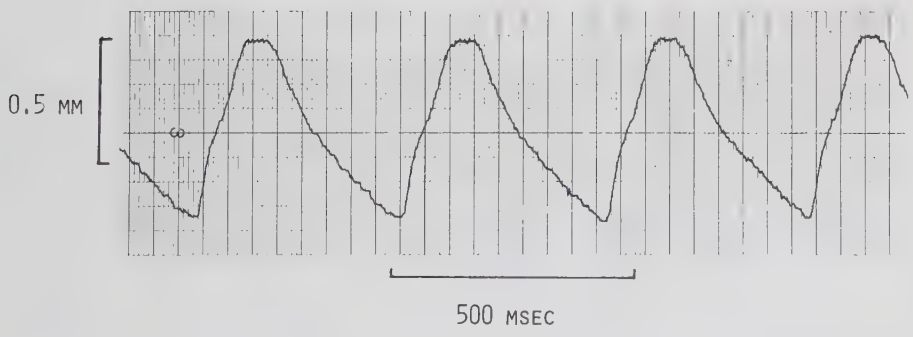

Fig. 2. Diameter pulse wave curves recorded from the fetal descending aorta at 36 weeks of gestation.

Recording of fetal breathing movements

FBM are a normal phenomenon during the greater part of

fetal life. A characteristic feature of the human FBM is the great variability in rhythm, rate, and amplitude occurring, depending of a variety of physiological events and clinical interventions. FBM occur in longer or shorter sequences, with intervals of apnea. In the present study (paper III), fetal apneic intervals were arbitrarily defined as non-breathing periods lasting more than 6 seconds. Furthermore, breath-to-breath intervals were measured only during periods of continuous breathing; no fetal apneic intervals were included in the calculations.

Several methods have been employed in an attempt to quantify the breathing movements visualized on the screen of the real-time B-mode system (Maršál et al 1977). In the present study (paper III) the breathing movements were quantitatively recorded using the TD-recording system (Maršál et al 1976, Lindström et al 1977) developed especially for measuring FBM. Measuring of echo movements with the TD recorder is based on the principle of amplitude-dependent tracking, where the time (distance) to a particular echo within a gate is tracked as long as the amplitude of the echo exceeds a pre-set value (Maršál et al 1976). The system includes a real-time ultrasound scanner (ADR, Tempe, Arizona) with a 3.0 MHz linear array transducer. With the TD recorder, any of the imaging lines on the two-dimensional B-mode image can be chosen for measurement. Along this line, two electronic markers are used to select the echoes whose movements are to be recorded, i.e. echoes from the proximal and distal wall of the fetal chest. The first echo following the proximal marker starts a digital clock. This is then stopped by the echo next to the distal marker. The time between the two fetal chest wall echoes is measured digitally and a digital-to-analog converter produces an on-line signal corresponding to the momentary fetal chest diameter. Either the absolute value or the relative changes in the diameter can in this way be displayed and recorded. The TD

recorder is easily adjusted with a thumb-wheel switch for line selection, and two potentiometers for echo selection. All three controls are placed in a remote box.

The method has been calibrated in vitro and was dynamically tested in vivo (Maršál et al 1978). Continuous supervision of the target on the scanner screen ensures the validity of the signals. The ability of the equipment to measure diameter changes minimizes the influence of non-specific movements. However, there is still a certain risk of producing artefacts. During maternal breathing the movement of the abdominal wall may both dislocate the attached transducer and alter the angle of insonation (Maršál et al 1978). Furthermore, the validity of the signal derived from the distance measured depends on the presence of strong echoes from both the near and the far fetal structures, i.e. the distal chest or abdominal wall. Therefore constant supervision by the operator of the scanner screen is necessary to ensure an optimum insonation of the fetus in order to protect the recordings from artefacts.

Measurement of fetal heart beat intervals

Abdominal electrocardiography (ECG) offers the most accurate timing of fetal heart beats in order to determine the variability of the fetal heart beat interval (Wheeler et al 1978). The processing of the signals in commercially available instruments includes, however, various sources of error (Wheeler et al 1979). Different methods have been applied to compensate for the fact that, in commercial instruments using a blanking technique, fetal cardiac signals recorded via abdominal electrodes are lost when coinciding maternal QRS complexes are rejected (Wheeler et al 1978, Kariniemi et al 1979). The cardiotocograph used in paper IV worked on abdominally recorded mixed fetal and maternal ECG. The cardiotocograph removes maternal QRS

complexes, excluding coinciding fetal complexes. A pulse, interpolated linearly in time, was substituted for each fetal signal excluded. The variation in the fetal heart beat intervals (the standard deviation (SD) and the standard deviation of interval differences (SDID)) reported in paper IV is thus partly based on intervals duplicating the previous beat interval and influencing the subsequent interval. The beat-to-beat intervals of the fetal signals detected were evaluated by feeding the signals into a computer (PDP 8/E Digital Equipment Corporation). To exclude false intervals due to artefacts the rate of change between two successive intervals was set to 10% and likewise intervals less than 285 msec (210 beats per min) and intervals longer than 500 msec (120 beats per min) were excluded. Before the present study was carried out an attempt to evaluate the impact of this factor on the fetal heart beat intervals was made. In order to estimate possible error due to this blanking process a computer-aided simulation test was carried out. The duration of the fetal and the maternal QRS complexes was set to be 60 msec and 100 msec respectively at a constant maternal heart rate of 90 beats per min, and a FHR of 167 beats per min. When a fetal complex overlapped a maternal one, this was regarded as a collision between the two signals and a blanking was simulated by excluding the two signals and inserting one linearly. This occurred for 24% of the fetal complexes, as illustrated in Fig. 3.

In order to evaluate the consequences for the estimation of the true variability of the heart beat intervals imposed by the blanking procedure of the cardiotocograph used, the following calculation was performed. To a randomly chosen original sequence of digitally stored fetal QRS complexes, simulated maternal heart beat intervals of a constant duration (667 msec) were added and blanking was performed. The SD and the SDID for groups of

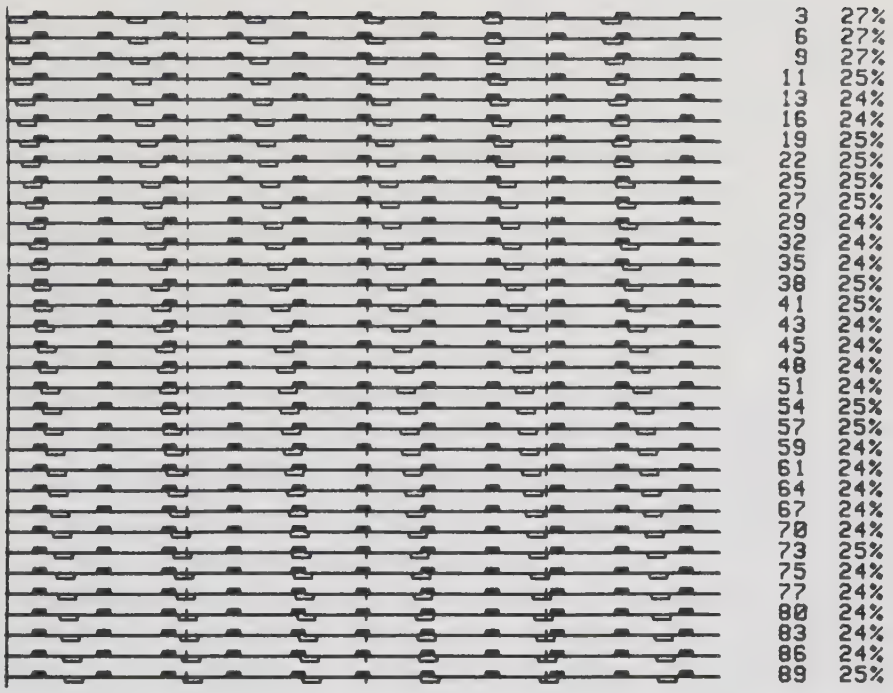

Fig. 3. A computer-drawn diagram of simulated coincidences between maternal (downward open deflections) and fetal (upward filled deflections) QRS complexes. The interval between the vertical lines denotes 1 sec, the phase difference between the horizontal lines is 4 sec. The duration of the maternal and the fetal complex is preset to 100 msec and 60 msec, respectively. The interval between the complexes is 670 msec (equivalent to 90 beats per min) and 360 msec (equivalent to 167 beats per min), respectively. The figures denote the cumulative numbers of coincidences (left column) and the rate of coincidences relative to the number of fetal complexes (right column).

75 consecutive intervals (the sample size representative for the 30-sec epochs used in paper IV) were calculated by computer from both the original sequence of signals and the blanked trace. This simulation demonstrated that the SD of the beat interval was increased by 3.1% by the blanking and interpolation, while the SDID was increased by 33.3%. For analysis of any error caused by the blanking process changing with the FHR, we compared the differences between the beat interval variation obtained from the original trace and that obtained from the blanked one at two different average interval levels (equivalent to 129 and 154 beats per min, respectively). No significant difference was found between the two different heart rate levels for either the SD or the SDID. A correlation analysis between the SD obtained from the original trace of beat intervals and that obtained from the blanked trace revealed a high coefficient of correlation ranging 0.99-1.00. The corresponding coefficients for the SDID were in the range 0.92-0.93. This evaluation revealed that the long-term variability index, the SD, was affected to a minor degree only by the blanking, but the process did produce a distortion of the absolute values of the SDID. The strong correlation, however, between the SDID before and after blanking demonstrates that the blanking process altered the numerical value of the index but retained the relative variation. This indicated that the conventional cardiotocograph could be used for its specific purpose, when the fetus acted as its own control and the same procedure was followed before and after a given test stimulus.

Measurement of blood flow in the fetal vessels

Many experiments have been performed with the intention of measuring the umbilical blood flow. Early studies (Dawes 1968) were made using exteriorized fetal lambs. The first measurement of umbilical blood flow in animal fetuses in

utero were made using the Fick principle using the diffusion-equilibrium technique (Meschia et al 1967). In the past, electromagnetic flowmeters (Berman et al 1976) have been used. All these methods are invasive, however, and not applicable to the human fetus *in utero*. The development of Doppler ultrasonic blood flow detectors has proved their usefulness in a number of areas, notably in connection with blood velocity measurements in superficial vessels. By combining real-time linear array ultrasonic technique and pulsed Doppler ultrasound it has been possible to quantify the blood flow also in deep-lying vessels such as the fetal descending aorta and the umbilical vein (Eik-Nes et al 1980, 1983).

The measurement of blood velocity using ultrasound is based on the Doppler effect, which implies that the frequency of a sound wave transmitted from a stationary source and reflected from a moving interface changes according to the velocity and the direction of the moving interface. The change in the frequency, called the Doppler shift, is directly proportional to the velocity of the moving interface. In the pulsed Doppler ultrasound mode a short burst of ultrasound pulses is allowed to return to the transducer before a new burst is transmitted (Eik-Nes et al 1983). The fetal blood flow in the present study (paper VI) was measured by the same method. The measurement of the blood flow in the abdominal aorta and the umbilical vein of the human fetus was accomplished by a combination of a 3 MHz real-time scanner and a 2.0 MHz pulsed Doppler instrument. The real-time scanner was calibrated to the velocity of sound 1 540 $m.s^{-1}$. To remove signals from slow-moving tissues in the path of the beam, a 400 Hz high-pass filter was used at the beginning. This filter, however, was found to eliminate considerable portions of the diastolic flow, thus erroneously decreasing the resulting mean aortic blood flow by nearly 30% (Maršál et al 1983, Griffin et al 1983). The high-pass

filter was therefore changed to a 100 Hz filter which does not significantly distort the diastolic portion of the blood flow. The Doppler transducer was attached to the real-time transducer at a fixed angle of 45^{o}. When recording the blood velocity, the real-time transducer was moved until it was parallel to the longitudinal axis of the vessel, thereby enabling correction of the recorded blood velocity for the angle between the Doppler beam and the vessel visualized on the B-mode screen. The pulse repetition frequency is shifted automatically from 9.5 to 5.2 kHz, depending on the depth range. The sample volume of the Doppler instrument is positioned at the depth which was previously measured in the real-time image. The adjustment of the sample volume position was checked by listening to the Doppler signal, by visual analysis of the Doppler spectrum on an oscilloscope screen and, when necessary, on a hard copy. The vessel diameter was measured from the real-time image on the scanner screen, using a TD recorder (Lindström et al 1977) and the vessel area, assumed to be circular, was calculated from the diameter. The volume blood flow was calculated from the blood velocity and was related to the fetal weight estimated from the sonically measured biparietal and the abdominal diameters and expressed in $ml.min^{-1}.kg^{-1}$ (Eik-Nes et al 1982).

The method has been tested in both *in vitro* experiments and *in vivo* investigations (Eik-Nes et al 1982, 1983). Simultaneous recording of the blood flow with an electromagnetic method and with the described Doppler technique in the abdominal aorta of a pig revealed a high coefficient of correlation between the two methods ($r = 0.91$). The main source of error was found to be error in estimating the vessel diameter. For vessels with a calibre between 6 and 8 mm, as found in the aorta in late pregnancy (paper II), an error of 0.4 mm in estimating the diameter will cause an 10% error in the vessel blood flow

value, which is of the same magnitude as found by others (Gill et al 1981).

Determination of COHb percentage and nicotine concentration

Brief description of the methods

Carboxyhemoglobin (COHb) in maternal blood was determined in a gas chromatographic system, with CO detected as methane by flame ionization according to the methods devised by Porter & Volman (1962) and Collison et al (1968). In preparing the COHb standard, the physically dissolved CO and the CO-refractory hemoglobin were considered (Sundström 1972). The normal percentage value of COHb in non-smokers with this method is 0.58 $\pm$ 0.28 (mean $\pm$ 2 SD). The coefficient of variation for a series of 10 reference determinations was 2.1%.

Nicotine was measured in papers III and IV by a method comprising gas-liquid chromatography and mass-spectrometry (Feyerabend & Russell 1980). The intra-assay coefficient of variation with this method was 8.0% and a control group of non-smokers had a mean value of 5 µg/l blood. In papers V and VI a slightly modified technique was used, based on toluene extraction and gas-liquid chromatography with nitrogen detection (personal communication, R. Lundgren, LEO, Helsingborg, Sweden). The values were corrected for a value of 2 $\pm$ 0.5 ng nicotine because of a contamination from the background of 2 ng nicotine.

MATERIAL

A total of 93 pregnant women participated on a voluntary basis in the studies (Paper II, III, IV, V and VI). All fetuses investigated were singletons in the 28th to 42nd gestational week, the estimation of gestational age being based upon early fetometry. The fetuses were normal at the time of investigation according to routine clinical

criteria, none developed distress during the subsequent parturition and the birth weights ranged between mean ± 2 SD of the local growth curves. The study protocols had been examined and accepted by the local ethical committee.

Fifty-seven women participated in the four smoking studies (paper III, IV, V and VI). All the women were habitual smokers with a daily consumption of 1 to 30 cigarettes, who were urged not to smoke for 12 hours before the study. In the studies on FHR, FBM and FM (paper III and IV) the investigations started at 1230 hours after the women had had a carbohydrate-rich lunch. Furthermore, care was taken to keep the blood glucose level of the women at a post-prandial level throughout the study. In order to compensate for the rest-activity periods with an average cycle length of 1 hours, which strongly influences the incidence of the FBM and the FHR, a 60 min control time and a 60 min post-smoking time was used. Glucose was determined in maternal venous blood collected at -60 min, -30 min, 0 min, +10 min, +30 min and +60 min. For determination of carboxyhemoglobin and nicotine blood was sampled at 0 min, +10 min and +30 min. In the studies on fetal pulse waves and blood flow (paper V and VI), the study protocol was slightly different with 15 min for settling down followed by a 10 min control period and a 45 min post-smoking period including recordings every five min. For determination of carboxyhemoglobin and nicotine in maternal blood in these studies, samples were taken at -10 min, +10 min, and +45 min.

RESULTS AND DISCUSSION

COHb percentage and nicotine concentration in maternal blood

The COHb percentage and the nicotine concentration were

measured in the maternal blood to ensure that the women had abstained from smoking prior to the study. Nicotine in particular is a good marker for this purpose, considering the half-life of only 40 min in the maternal circulation (Armitage et al 1975). Furthermore, the blood analyses were performed ensure that the women were inhaling the tobacco smoke and thus obtaining a measure of the strength of the stimulus. The effects of smoking on the maternal values of nicotine and COHb in papers III, IV, V, VI were quite similar and consistent with the response found in earlier studies (Gennser et al 1975, Armitage et al 1975, Quigley et al 1979). The pre-smoking values and the approximately parallel rise in COHb and nicotine show that the endeavour to adhere to the study protocol was on the whole successful. A significant correlation was found between the average daily cigarette consumption stated by the women and the COHb percentage in the control period. No other correlations were found with respect to the COHb percentage and the parameters FBM, FM, FHR, diameter pulse wave and fetal blood flow, respectively. This is not surprising, as the diffusion of CO across the placenta is slow. During the first hour of maternal CO exposure, fetal COHb concentration has been found to show little change and fetal COHb equalled maternal concentration first after 6 hours (Longo 1977). These studies were carried out in pregnant sheep. For ethical reasons such studies on CO exchange rates are impossible in the human fetus, but the calculated theoretical relation of fetal/maternal COHb concentration in the human subject was very similar (Hill et al 1977).

Nicotine crosses the placenta rapidly (Suzuki et al 1974, Manning et al 1978). In the pregnant ewe, fetal concentration was found to equilibrate with the maternal concentration after 5 min (Manning et al 1978). In the fetus of rhesus monkey a maximum in the nicotine concentration was seen 16 min after the intravenous administration of

nicotine to the mother (Suzuki et al 1974). The changes in the different parameters within the period 5 to 25 min after the onset of smoking in papers III, IV, V, VI coincided with the increase in nicotine concentration in the animal fetuses mentioned above. The elimination rate of nicotine from the maternal blood was closely correlated to the attained maximum level (paper III), as has also been demonstrated in men in arterial blood (Armitage et al 1975). Habitual smoking induces the enzymes responsible for the metabolism of nicotine (Beckett & Triggs 1967) and might therefore occasion a more rapid elimination of nicotine in women with higher nicotine intake. The significant correlation between the nicotine concentration and the increase in apneic epochs after smoking and the breath-to-breath intervals, respectively, points to a causal connection between nicotine and the response of FBM. In paper IV, however, no significant correlation was found between the heart beat interval and the SDID on the one hand, and the nicotine concentration after smoking on the other, which suggests that substances other than nicotine in the smoke might also affect the fetal heart. This assumption has been supported by studies in adults showing an increased heart rate even after smoking cigarettes with an ultra-low nicotine content (Rabinowitz et al 1979). The findings in papers V and VI are mutually contradictory, as in paper V we found significant correlations between the nicotine concentration and the fetal heart rate which not could be verified in paper VI. These discrepancies are not explained, but the different results in the three papers (IV, V, VI) might be due to random variation with other substances in the cigarette smoke responsible for the changes found in fetal heart beat intervals.

Conclusion

COHb is believed not to contribute to the acute responses

of the fetus to maternal smoking of one cigarette, as the diffusion across the placenta has been found to act too slowly. The COHb percentage was found, however, to reflect the number of cigarettes smoked during the day. The nicotine concentration was found to correlate with the change in breathing rate and the number of apneic epochs. The results concerning possible correlations between nicotine concentration and fetal heart beat intervals were contradictory. No correlations were found between nicotine concentration and the parameters of diameter pulse waves and flow in the descending aorta and the umbilical vein. Components other than nicotine might therefore also be responsible for the influence of the fetal cardiovascular system.

Fetal breathing and gross movements and maternal smoking

FBM and smoking

The immediate effects of cigarette smoking on FBM and FM were studied in paper III. The maternal blood glucose concentration was maintained at a constant postprandial level throughout the study. After smoking, a significant increase in rate of FBM appeared, together with a reduction in the short-term variability of the breath-to-breath intervals. No change was seen in the incidence of FBM. The number of epochs without FBM or fetal trunk and limb movements increased after maternal smoking, thus indicating a change in the spacing of these activities.

The finding of an unchanged incidence of FBM after smoking is contrary to the results in two earlier reports with use of A-mode ultrasound, both describing a reduction in the incidence of FBM (Gennser et al 1975, Manning & Feyerabend 1976). This discrepancy may be explained in part by the limitations of the previously used A-mode technique (Farman et al 1975) and by differences in methodology between the aforementioned studies and our study (paper

III). The incidence of FBM has been shown to display several natural rhythms. Continuous measurements of human FBM for 24 hours using real-time ultrasound showed a significant increase in breathing activity during the second and the third hour following meals, i.e. at 10 a.m., 2 p.m., and 7 p.m. (Patrick et al 1978). In the study by Roberts et al (1979) the above-mentioned findings were confirmed, but considerable intra- and interindividual variation in the amount of FBM was seen. The overall incidence of FBM was 31% and 37% during the day. Junge & Walter (1980) analysed fetal behavioural states using records of fetal heart rates and fetal motor activity. A complete cycle (quiet sleep + active sleep) lasted for 75 min. During periods of quiet sleep which lasted for 20 min, FBM were present for 13.8% of the time, but in 50% of the periods, no FBM were found. Hill et al (1983) reported that FBM may be absent for as long as 108 min. Gennser & Maršál (1979) found large variations between the incidence of both the FBM and the FM during recordings at four times a day. Because of these fetal biorhythms, a sufficiently long observation time is necessary for examination of FBM and FM in late pregnancy (Maršál 1982). This requirement was not fulfilled in the study by Manning & Feyerabend (1976). For adequate results, the recording time must therefore exceed the length of at least one complete fetal activity cycle. This suggests that the recording time should be at least 70 to 80 min (Gennser & Maršál 1979).

The diurnal variation of FBM was found to run parallel with the blood glucose profile (Patrick et al 1978) and a positive correlation between the maternal blood glucose level and the incidence of the FBM has been demonstrated (Roberts et al 1979). Natale et al (1978) studied the FBM following the maternal ingestion of 50 g oral glucose. The incidence of FBM increased from 23.2% to 58.9% 105 min following the oral glucose load. After intravenous injection of 25 g glucose a significant increase in the in-

cidence of the FBM occurred 25 min after intervention, but no changes in breathing rate or breath-to-breath interval variability appeared (Goodman 1980). This positive correlation, on the other hand, between the glucose concentration and the incidence of FBM has made it necessary to keep the glucose concentration at a constant level throughout the study period. This was only partly successful in the study by Manning & Feyerabend (1976) as a slight fall in the glucose concentration was observed throughout their study, the concentration being significantly different from the presmoking values 60 min after the onset of smoking. In the present study by us (paper III) a demand for a sufficiently long period of recording was met. Moreover, care was taken to keep the maternal blood glucose level at postprandial values throughout the study. The measuring technique with continuous observation of the FBM on the scanner screen and the use of the TD recording technique to monitor objectively and FBM further ensures the validity of the signals obtained. In the study by Manning & Feyerabend (1976) a significant reduction in the incidence of FBM of 43% was found after maternal smoking of two cigarettes. The incidence of FBM during the control period was, however, as high as 69.7% of the time, which is more than twice the amount of FBM observed by means of real-time scanners (Patrick et al 1978). According to Boddy (1976) an estimated 20 to 25% of recordings obtained with A-scan technique are so encumbered with artefacts as to be uninterpretable. Thus the discrepancy between the results obtained with the A-mode and the B-mode technique is in part attributable to the inadequacy of the A-mode monitoring technique. The reduced breathing rate found in paper III is similar to the findings of Thaler et al (1980). In this study, using a continuous Doppler ultrasound method, a small but significant increase in the breathing rate was found, whereas the incidence of FBM did not change. The increased breathing rate found in the human fetus after maternal smoking is similar to the

findings in adults with tachypnea after nicotine administration (Heymans et al 1931). The changed breathing rate could not have been caused by the glucose administration itself, as glucose has earlier been found not to affect either the breathing rate or the variability (Goodman 1980).

Dawes et al (1973) demonstrated that acute hypoxia has the immediate effect of inhibiting episodic fetal breathing in the fetal lamb. Boddy et al (1974) observed that fetal hypoxia produced by administering a hypoxic mixture to the ewe resulted in a decrease in or complete cessation of FBM. Several drugs have been found to interfere with FBM (Wilds 1978, Lewis & Boylan 1979, Hill et al 1983). Murata et al (1981) studied the effects of various catecholamines on the FBM. Following injection of norepinephrine intravenously in the fetus of rhesus monkey, a depressant effect was found on the incidence of FBM, while no significant changes were observed after administration of epinephrine. Nicotine administration causes a sympathomimetic response, by stimulating the sympathetic ganglia and also by central reflex actions, as well as indirectly as a result of the release of catecholamines from the adrenal medulla and chromaffin tissues (Armitage 1965). Nicotine administered to the pregnant ewe depressed the breathing activity in the lamb, concomitantly with a significant fall in the arterial PO_2, whereas direct injection of nicotine into the fetal circulation did not affect the incidence of FBM recorded from a tracheal pressure catheter (Manning et al 1978). Maternal injection of 10 to 20 mg nicotine produced a rise in fetal blood pressure and a fall in fetal heart rate. This might indicate that in the fetal lamb the action of nicotine in depressing FBM is mediated by reducing uterine blood flow, with consequent fetal hypoxia (Manning et al 1978). The dosis of nicotine used in this study, however, is about twenty-fold larger than that absorbed in humans after

smoking one cigarette. Even when differences in sensitivity to nicotine among various species are taken into account the dosis in the above-mentioned study seemed to be unphysiological. The responses after maternal smoking in man are more likely to be a nicotine-induced fetal reaction rather than a reaction caused by hypoxia. This is supported by the unchanged incidence of FBM after smoking and the increase in FHR and breathing rate similar to the findings in adults after smoking.

FM and smoking

Maternal perception of FM has been suggested as a useful way of monitoring fetal well-being (Sadowsky & Yaffe 1973). However, maternal counting of fetal movements might show subjective variations, objective methods of recording fetal movements, including strain-gauge (Wood et al 1977), a tocodynamometer (Timor-Tritsch et al 1976), piezoelectric crystals (Lindström et al 1981) and real-time ultrasound (Gettinger et al 1978, Hertogs et al 1979) have all been applied.

There is disagreement regarding the response of the human fetal gross movements after maternal smoking. In our study using real-time ultrasound (paper III) an unaltered incidence of FM was found, but the number of epochs without fetal trunk movements increased. Earlier a depressant effect of smoking on the number of FM had been reported (Wood et al 1979, Thaler et al 1980). These studies were carried out with subjective recordings of the FM felt by the mother. In paper III the incidence of the FM, i.e. the relative extent of observation time occupied by FM, was measured, as this has been claimed to be more reliable than counting the number of movements (Gettinger et al 1978). The unchanged incidence after smoking, together with a greater degree of clustering of the movements, does not conflict with the findings by others (Wood et al 1979,

Thaler et al 1980), as it can be assumed that the mother's ability to distinguish fetal movements from one another is impaired when these movements are grouped into uninterrupted periods. Furthermore, the glucose concentration - or its increase - is known to play no part in the pattern of FM, as intravenous injection has been found not to affect the incidence of fetal gross movements up to 6 hours after administration (Bocking et al 1982). On the other hand, only a part of the fetal body can be visualized on the real-time ultrasound scanner screen during the recordings. This might cause one to overlook smaller, isolated limb movements. Larger movements affecting one or all parts of the fetus are easily recognized, however, as the whole body, even the visible part, is then moving.

Conclusion

In the study it was demonstrated that the responses to maternal smoking in the human fetus consist in an unchanged incidence in FBM and an increase in breathing rate together with an increase in FHR. The findings in animal experiments of a reduction or a complete cessation of fetal breathing after administering a hypoxic mixture to the mother has been found to be accompanied by a concomitant decrease in PO_2 and a fall in fetal heart rate. The findings by us does for that reason not support the theories of smoking altering the fetal oxygenation, but the changed breathing rate and clustering of the fetal movements, more point to a direct central effect of some components in the smoke, thereby possibly also altering the fetal behavioural state.

Diameter pulse waves in the fetal descending aorta

Method

By applying the phase-locking technique used in the

present series of investigations (paper I, II, V) we have shown for the first time that it is possible to make non-invasive recordings from deep-lying vessels in the human fetus. The phase-locking technique was tested thoroughly in both in vitro and in vivo experiments. At a repetition rate of 2.56 kHz a maximum tracking velocity of 438 mm/sec at 10 cm depth was found. The minimal detectable movement of the ultrasound echo complex was found to be 50 μm, which by far exceeds the axial resolution of approx. 1 mm of the real-time scanner (ADR, Tempe, Arizona). The validity of the measuring capacity of the echo-tracking equipment was tested against an independent optical method. The measurements revealed a highly correlated linear relationship between the two apparatuses (r=0.99).

Tilting of the transducer away from the long axis of the aorta will falsely increase the measured diameter of the vessel and its changes. This error was minimized, however, by the fact that during continuous visualization throughout the recording, the transducer was kept parallel to the course of the aorta. On the other hand, a rapid tilting of the transducer diminishes the reflection intensity of the ultrasonic beam from the vessel wall. This causes insufficient locking of the echo-tracker, which slips from its echo for one or several wavelengths, and will therefore easily be detected. This is also seen when the reflected echo signal faded for reasons other than altering of the insonation angle. A displacement of the vessel in a plane perpendicular to the beam and to the linear array transducer is difficult for the operator to detect. However, the width of the beam (approx. 1 cm) in relation to the vessel's diameter minimizes the error of small displacements in this plane to presumably negligible proportions.

The phase lock system must for physical reasons lock on to a zero crossing within an echo complex, thus at a distance

of at least one half wavelength from the inner surface of the aortic walls. At a sound speed of 1,540 m/sec and a transducer rate of 3.0° MHz, this leads to a minimum overestimation of the true diameter by 0.5 mm. The error is partly compensated by the fact that the equipment used was calibrated for a sound speed of 1.540 m/sec, whereas the propagation velocity of ultrasound in blood at 37°C has been measured at 1,580 m/sec (Bakke et al 1975). When the diameter of the aorta was calculated from the present data in paper II as the mean of the systolic and diastolic diameters, our values from the latter half of the third trimester tallied well with the corresponding measurement of the fetal aorta performed with subjectively placed electronic calipers in a real-time scanner (Maršál et al 1983). From the 28th to the 35th week, however, recordings gave slightly lower diameter values than those measured with calipers. As in the latter investigation the diameter was calculated from the outer aspect of the proximal wall to the inner aspect of the distal wall, the discrepancy found suggested that the relative thickness of the image of the vessel walls early in gestation is greater than near term.

Physiology

(a) Pulse amplitude

In paper II we have shown that the mean amplitude of the diameter pulsations in the fetal aorta was similar throughout the third trimester, but that as the apparent diastolic diameter increased, the relative pulse amplitude decreased from 22% to 16%. The pulsatile area change during the cardiac cycle was, on average for the entire period, 46% of the area in diastole, increasing by 29% from weeks 28-35 to 36-40. In adults the pulsatile diameter change in the aorta and the carotid artery, using the strain gauge technique, is reportedly only 1-8%

(Greenfield & Patel 1962, Greenfield et al 1964), whereas pulsations measured by means of ultrasound (Arndt et al 1968) or angiography (Leitz & Arndt 1967) in the carotid artery are somewhat higher, but still lower than the values found in the fetus. The pulsatile diameter change in the fetus found by us (paper II), on the other hand, accords well with observations obtained with M-mode ultrasound on the human fetus at term (Chiba et al 1979). Our observation concerning the pulsatile change in cross-sectional area during the cardiac cycle (paper II) was two to three times as great as the change found in the adult aorta using strain gauge technique (Greenfield & Patel 1962) or real-time ultrasound (Lusby et al 1981). This difference might suggest a better compliance and/or greater pulse pressure changes in the fetus than in the adult. Furthermore, the decrease in the relative amplitude of the pulsations throughout the third trimester might reflect an increase in mean arterial blood pressure impairing the compliance of the vessel walls. Although the arterial pressure in the human fetal aorta is not known, blood pressure in several animals has been found to increase during pregnancy (Dawes 1968).

An intimate co-variation has been demonstrated between heart rate and cardiac output; thus in normal adults, left ventricular ejection time was found to vary inversely with heart rate and directly with stroke volume (Weissler et al 1961). In paper II a positive linear relationship was found in the human fetus between the amplitude of the aortic diameter pulsations, reflecting the ventricular stroke volume, and the preceding beat interval below 550-600 msec. This observation contradicts the findings of Rudolph & Heyman (1976), who found a positive linear relationship between fetal heart rate and ventricular output in the lamb. This might indicate that in the fetal lamb the heart has a limited ability to increase its stroke volume when its rate is reduced. In the adult

animal, however, stroke volume adjusts to changes in heart rate over a wide range, thus maintaining a relatively constant cardiac output (Guyton 1981). This accords with our findings in the human fetus (paper II) and with recent findings in the fetal lamb, where a highly significant positive relationship was demonstrated between end-diastolic volume and stroke volume (Anderson et al 1982). Moreover, left ventricular output remained unchanged over a wide range of spontaneous heart rates within 114 to 180 beats/min, demonstrating that the Frank-Starling relationship is both operative and effective in the fetal lamb heart (Kirkpatrick et al 1976). Our finding in the fetus (paper II), suggesting that the Frank-Starling relationship is effective also during human fetal life, recently corroborated by Maršál et al (1983). Pulsed Doppler measurements in the descending aorta of the human fetus demonstrated that prolonged beat intervals augment the flow velocity, being an indication of stroke volume (Hatle & Angelsen 1981). Thus, in contrast to the vagal stimulation studies by Rudolph & Heyman (1976), spontaneously occurring slow heart rates were not associated with a fall in cardiac output in either the fetal lamb or the human fetus. For beat intervals exceeding 550-600 msec (110 to 100 beats/min) we found no further increase in the pulse amplitude. A similar observation was reported in the paper of Murata & Martin Jr (1974). With fetal heart rates below 115 beats/min, no further prolongation of the left ventricular ejection time was observed, suggesting that the maximal stroke volume is achieved in the human fetus at heart rates of 110-115 beats/min.

(b) Propagation velocity

Calculation of the propagation velocity of the pulse wave with the phase-locking equipment included registration of the propagation time at two different points in the aorta, with a slight time shift between the two recordings (paper

II). The ideal equipment for the purpose of measuring the propagation velocity would allow the use of a technique giving simultaneous recording of the propagation time at two levels (an improved equipment is under construction). However, any variation in the propagation time was minimized by recording the pulse waves only during periods of fetal rest with the fetus in steady state. In spite of the technical imperfection, the results are nevertheless indicative of a clear trend. The propagation time measured comprised both the pre-ejection time (PEP) (Hawrylyshyn et al 1982) and the propagation time proper, along the aorta. Most studies have reported that PEP is influenced by gestational age and heart rate (Organ et al 1980, Sampson 1980, Hawrylyshyn et al 1982). The propagation time measured in paper II was therefore corrected for differences in fetal heart rate according to the formula published by Organ et al (1980). Moreover, to reduce the variation between fetuses of different ages the propagation time was defined as beginning with the onset of the Q-wave-and not the R-wave- as the QRS complex has been found to increase in time with advancing gestational age (Hawrylyshyn et al 1980). By estimating the pulse wave velocity (paper II) two interesting conditions were revealed. First, the pulse wave velocity, ranging 1.35 to 2.89 m/sec, was about one-third of that found for adults (Hallock 1934, Eliakim et al 1971). Our values are in contrast to the finding of a mean velocity of 0.90 m/sec in the last trimester of human fetuses reported recently (Chiba et al 1979). In this study, however, the authors had included the PEP in the propagation time of the pulse wave along the aorta, thereby reducing the pulse wave velocity considerably. Moreover, the length of the vessel from the aortic valves to the measuring point was only roughly estimated. By correcting the value of propagation time by a mean PEP value in the third trimester (Organ et al 1980), a propagation velocity of 2.79 m/sec was achieved, this value being consistent with those obtained in the

present study (paper II). Secondly, the velocity increased with advancing gestational age, which might reflect, among other factors, a decreasing compliance of the fetal vessel wall. This could be due to a structural rearrangement of the vessel wall, but anatomical studies have revealed that the number of elastic fibres in fetal aorta is the same as found in the adult aorta (Harkness et al 1957). In normal subjects a linear correlation was earlier found between mean arterial blood pressure and pulse wave velocity (Frank 1905) as well as between diastolic and systolic blood pressure and likewise the pulse wave velocity (Sands 1925). Therefore, the increased pulse wave velocity might reflect an increasing arterial blood pressure during the third trimester, straining the vessel wall and thereby diminishing its compliance. This would accord with the findings in various species of a gradual rise in mean arterial blood pressure during fetal life (Dawes 1968).

(c) Form analysis

In paper II we reported that the pattern of the diameter pulse curve recorded from the fetal aorta was constant under regular heart rate conditions. The initial phase of the upstroke was quick, while the latter part of the systolic portion was dome-shaped. A well-defined systolic reflection point devided the pulse wave into early and late systolic phases. These results are supported by the findings in healthy adult humans where a similar well-defined reflection point has been demonstrated (Murgo et al 1980) and by the findings in dogs where aortic pressure was found to rise by 50% of the pulse pressure when less than 1 ml of the stroke volume had been ejected from the heart (Noble et al 1967). This first part of the rising slope, expressed as the maximum increment velocity (MIV), reflects mainly the force of the cardiac contraction (McDonald 1974). This parameter was found not to alter with gestational age or the preceding beat interval, but

it did increase with the distance from the heart. The crest time and the inclination time, both describing the systolic part of the pulse curve, were both dependent on and positively correlated to the preceding pulse length. The visco-elastic property of vessel walls is reflected in their pattern of pulse curves. In the presence of obstructive arterial disease, the crest time and the inclination time are prolonged (Winsor & Karpman 1959). Considering that the crest time and the inclination time both decrease in distal direction along the arterial system (McDonald 1974), our observation of much lower values relative to the cycle length in the fetal aorta, than the corresponding values from peripheral vessels in normal adults, suggests a greater degree of compliance in the fetal than in the adult aortic wall.

Conclusion

Cardiac output is adjusted by changes in one or more of four principal factors that determine myocardial function. These are preload, myocardial contractility, afterload, and heart rate. In the human fetus the complexity of the diameter pulse curves was realized and analyses were therefore based on already established methods in clinical physiology. Evidence has been found that the Frank-Starling relationship is valid also in the human fetus. Moreover, pulse amplitude and maximum increment velocity seem to be promising non-invasively monitoring the condition of the human fetal cardiovascular system.

Fetal heart beat intervals and maternal smoking

The purpose of the study (paper IV) was to analyse the immediate effects of maternal smoking on the fetal heart beat intervals and their variability. The fetal heart beat intervals were monitored by abdominal electrocardiography for 60 min before and 60 min after smoking one cigarette.

The mean beat intervals, their long-term variation (SD) and short-term variation (SDID), calculated for 30-sec periods, showed a steady state during the control period. After smoking, the mean beat interval and the SDID decreased transiently by maxima of 11% and 17%, respectively, within the first 15-20 min after the onset of smoking. The long-term variation, on the other hand, did not change after the maternal smoking. The decrease in the mean beat interval has been confirmed in the two later papers (V and VI) and was in agreement with earlier studies (Sontag & Wallace 1935, Doerfel 1952, Quigley et al 1979). In our study, care was taken to compensate for the rest-activity state variability by making the study and test periods as long as 60 min (Hoppenbrouwers et al 1981). Periods with low heart rate variation are found to last up to 40 min near term in normal pregnancies (Visser et al 1981). A sample size of 30 sec was chosen, as this time base has been found the most appropriate for this specific purpose (Organ et al 1978, van Geijn et al 1980). In the human fetus, accelerations in heart rate were found to be closely associated with fetal movements and a decrease in beat-to-beat variation (Dawes et al 1981). In our study (paper IV) a decrease in the short-term variability, expressed as the SDID (Wheeler et al 1979), was found to appear with the rise in heart rate. This accords partly with the findings by Kariniemi et al (1982) where a significant correlation was found after maternal smoking between maternal heart rate and the mean interval index, describing the short-term variability component. In the same study a significant correlation was found between the maternal systolic blood pressure and the mean differential index, describing the long-term component (Kariniemi et al 1982). In paper IV no significant changes were found with respect to the SD, another measure of the long-term variability (Dalton et al 1977, Wheeler et al 1979). The results in the two studies are not directly commensurable, as in the one study the results were expressed as correla-

tions between the parameters (Kariniemi et al 1982) while in the other study (paper IV) the results were presented as absolute changes of the individual parameters. Differences in the study protocol, the various expressions used for the long-term variability, or different inhaling behaviour, may also be responsible for the disparity, as no correlations were found to the fetal heart rate in the study by Kariniemi et al (1982).

The presence of fetal heart rate variability appears to be a favorable factor regarding fetal status (Paul et al 1975). Loss of variability antepartum is indicative of a compromised fetal environment (Hammacher et al 1968, Flynn & Kelly 1977). Conflicting opinions have been expressed in the literature about possible correlations between heart rate and its variability. In the fetal lamb, most extensively studied, heart rate was found to decrease and variability to increase with advancing gestational age. During the circadian rhythm of rest and activity states there is a rise in both fetal heart rate and heart rate variability from quiet to active periods (Dalton et al 1977). Hypercapnia causes no significant changes in heart rate, but a rise in variability. Recently, by using autonomic blocking agents in chronically catheterized fetal lambs, no significant relationship was found between changes in heart rate and changes in variability (Dalton et al 1983). Concerning the human fetus it has often been suggested that heart rate variation is reduced when the mean heart rate increases (Yeh et al 1973, van Geijn et al 1980). Undoubtedly, beat-to-beat variation decreases immediately when the heart rate rises above the baseline in an acceleration (Dawes et al 1981). The same phenomenon has been found over a longer period of time (64 min) but with a wide scatter between the fetal heart rate variation and the pulse intervals (Dawes et al 1982). When fetal heart rate and heart rate variability were viewed in relation to changes in activity states, the two parameters

changed in the same direction (Wheeler & Murrills 1978). The contrary view was obviously expressed when stating that, both in the human fetus and in the fetal lamb, the higher basal heart rate is, the lower is the short-term variability (de Haan 1977). Beat-to-beat variation in the human fetus seems to change in a complex fashion to different physiological stimulations. There seems to be no reason why the two variables should be related to each other in a simple way in the human fetus. It has been confirmed that the variations in the heart rate in the human fetus are of the same order of magnitude as in the fetal lamb and that multiple rhythms are present (Dalton et al 1977). Confusion in this area can only be avoided by applying precise definitions of measured parameters and, in view of the apparently complex relationship between the mean fetal heart rate and its variation, expressions which combine the two need to be formulated with care (Wheeler et al 1979).

The myocardium is stimulated simultaneously by the parasympathetic and the beta-sympathetic nervous system. The acute responses to hypoxia have been investigated in a variety of species (Dawes 1968). In the fetal lamb the immediate effect of induced maternal hypoxia on the cardiovascular system is an increase in blood pressure with a concomitant fall in heart rate, parallel to the decrease in PO_2 (Cohn et al 1974), whereas a persistent increase in heart rate variability has been demonstrated (Stånge et al 1977, Dalton et al 1977). An inverse relationship between fetal $tcPO_2$ and fetal heart rate variability found in the human fetus during labour points in the same direction (Willcourt et al 1981).

Nicotine administered intravenously to a rhesus monkey mother was followed by hypoxemia and a parallel decrease in heart rate. In the more mature fetuses acidemia developed at the same time (Suzuki et al 1971). The doses of

nicotine used, however, is about 20 times as great as the dose absorbed after smoking one standard cigarette containing 1.6 mg nicotine. In the adult, smoking results in adrenergic activation (Quigley et al 1979) as evidenced by the elevation in maternal plasma norepinephrine and epinephrine levels following maternal smoking. Administration of epinephrine and norepinephrine to the pregnant rhesus monkey has been investigated with regard to alterations in the performance of the cardiovascular system and the acid-base state of the fetus (Adamsons et al 1971). Both of the catecholamines were found to produce severe asphyxia of the fetus when administered separately to the mother. However, only when larger doses of catecholamines were administered, a fall in fetal oxygenation was observed, with a concomitant fall in the fetal heart rate. The doses were 10 times greater than the amount found to reduce the uterine blood flow by 42% in the pregnant ewe (Clapp 1979). It is not self-evident that the decreased short-term variability demonstrated in paper IV can be taken as a sign of fetal compromise. The persistent presence of fetal heart rate accelerations during the first 15 min after smoking, where the changes were seen, speaks against a smoking-induced hypoxia in the fetus. This is consistent with a previous work demonstrating that, in chronically smoking pregnant women, one cigarette did not immediately increase the incidence of non-reactive non-stress test (Barrett et al 1981). On the other hand, the finding in the control period of a higher mean fetal heart rate in heavy smokers than in light smokers suggests a chronic effect of smoking on the regulation of the fetal heart (paper IV).

Conclusion

In paper IV the acute responses of the pacing the fetal heart to maternal smoking were evaluated. A significant decrease in heart beat intervals and a decrease in short-

term variability has been found. The findings were not interpreted as the result of an impaired fetal oxygenation, for two reasons. First, the cardiotocograms did not lose their signs of reactive pattern. Second, the increase in the heart rate and the decrease in short-term variability are contrary to the response found in the fetus with an acutely compromised utero-placental circulation. On the other hand, some chronic influence of the maternal smoking on the fetal heart rate may not be denied, as evidenced by the higher fetal heart rate in heavy smokers than in light smokers.

Circulatory changes in the fetus after maternal smoking

Diameter pulse wave

In paper V, we demonstrated that after the maternal smoking of one cigarette the level and the waveform of the diameter pulse curve in the fetal aorta changed markedly 3 to 25 min after the onset of smoking. The apparent diastolic diameter and pulse amplitude increased, while the ascending part of the curve increased in slope and decreased in duration. The diastolic part of the curve, the late decremental velocity, was reduced, and during the same period a reduction in the propagation time of the pulse curve along the aorta was found. Even when the parameters of the pulse wave form were expressed relative to the heart rate the findings after smoking were significantly different from the presmoking values. Non-invasively obtained data on the diameter changes in the human fetal aorta were previously not available, for technical reasons. The results in paper V have therefore to be compared with results obtained from animal experiments or from studies on human adults. The pulsatile amplitude of the diameter which to some extent reflects the stroke volume (Rushmer 1955, Guyton 1981) increased by approximately 14% after maternal smoking (paper V). This accords with an increase

of nearly the same magnitude in the end-diastolic dimension of the heart, or preload, found in healthy subjects smoking one high-nicotine cigarette (Rabinowitz et al 1979). Also in animal experiments an increase in cardiac output was found after catecholamine infusion (Rosenfeld & West 1977, Monheit et al 1983). A linear relationship has earlier been demonstrated between stroke volume of the left ventricle, intravascular pulse pressure, and aortic diameter pulsations under steady-state conditions (Rushmer 1955, Guyton 1981) and during catecholamine administration (Barnett et al 1960). An increase in stroke volume of the fetal heart following maternal smoking is further suggested by the increase in maximum velocity of the aortic blood flow (paper VI), as this is considered to be a measure of stroke volume (Hatle & Angelsen 1981). The dilatation of the descending aorta (paper V, paper VI) might be the result of two opposing forces. Sympathetic stimulation of the aorta in cats, and intravenous injection of norepinephrine in the rabbit both produce constriction of the aorta (Aars 1971, Pagani et al 1975). However, nicotine and/or catecholamine action also will counteract the contraction of the aorta via an increased peripheral resistance with a raised intravascular pressure. In the human fetus the observed dilatation of the descending aorta suggests that the latter mechanism predominates. The findings are further supported by a less steep descending slope of the pulse curve, reflecting an increased pulse pressure, or afterload, which is similar to the findings in adult smoking humans (Rabinowitz et al 1979, Timisjärvi et al 1980).

Smoking has recently been shown to increase the pressure wave velocity in the arterial system in normal subjects (Koch et al 1980). It is an open question whether the shortened pulse propagation time after smoking in the fetus (paper V) was caused at least partly by an increased pulse wave velocity, as the propagation velocity was not

measured. It is obvious from earlier measurements that PEP constitutes the major part of the propagation time. In several studies on the fetus, PEP has been found to decrease in response to acute hypoxia (Hawrylyshyn et al 1982). Cigarette smoking in normal subjects has also been found to reduce PEP (Jain et al 1977). The release of catecholamines from the fetal adrenal medulla concomitant with smoking results in increased myocardial contractility and a shortening of PEP. Thus, both an induced acute fetal hypoxia and nicotine administration will cause a shortening of PEP. Catecholamines are believed to be released in stress-related situations and also under hypoxic conditions. This is one of the reasons why it is difficult in human studies to separate the responses due to hypoxia from the responses due to pure nicotine and/or catecholamine effects in the fetus. Most of the reduction in PEP occurred after the onset of the first heart sound in the phonocardiogram, thereby excluding changes in the electromechanical delay as a major factor (Harris et al 1967). The shortening of PEP may therefore mainly be a result of a shortened isovolumetric contraction phase, reflecting a positive inotrope action on the myocardium. In the study by Rabinowitz et al (1979) cigarette smoking in adults was found to heighten myocardial contractility. A similar mechanism then might elicit a shortened proper PEP interval in the fetus, reflected by the reduced propagation time (paper V), although some influence of fetal hypoxia cannot be completely ruled out. An increase in myocardial contractility of the fetal heart in connection with maternal smoking is supported by the findings of an increased mean blood flow velocity in the fetal descending aorta (paper VI) and the increase in the velocity of the ascending slope of the pulse curve (paper V). The role of catecholamines in the augmentation of myocardial function is evidenced by the demonstration by Anderson et al (1980) that infusion of the betareceptor agonist isoprenaline in the fetal lamb caused striking changes in ventricular

systolic characteristics, with an increase in the rate of ventricular ejection.

Fetal blood flow

In paper VI the fetal blood flow was measured in the aorta and the umbilical vein after maternal smoking, combining real-time ultrasonography and pulsed Doppler technique. A transient increase in aortic and umbilical blood flow were registered, as characterized by the increase in the mean and maximum blood velocity, and the vessel diameter. Few studies have previously been performed concerning the acute circulatory responses of the human fetus to maternal smoking. Most papers have evaluated the responses of the fetal heart rate (Sontag & Wallace 1935, Doerfel 1952, Cloeren et al 1974, Quigley et al 1979) or the heart rate variability (Cloeren et al 1974, Kariniemi et al 1982). The findings in paper VI are contradictory to those reported by Jouppila et al (1983). In this study, aortic and umbilical blood flows were measured with a similar technique as in paper VI, but no changes in the blood flow were found. However, the design of the study was different; measurements of nicotine or COHb were not performed to ensure that the women had in fact inhaled the tobacco smoke. In fact, no changes were found in the maternal or the fetal heart rates between the control and test periods, indicating that a different smoking technique was used. Moreover, measurements were only performed immediately after the cessation of smoking.

The responses of the intervillous blood flow to smoking investigated in two studies gave mutually contradictory results (Cloeren et al 1974, Lehtovirta & Forss 1978). In the former study using a radioactive isotope technique with In-113m the blood supply to the placenta was not decreased. In the second study, cigarette smoking caused an acute decrease of 21% of the intervillous placental

blood flow, measured by the intravenous Xe-133m radioactive method. In parallel, an increase in maternal heart rate and blood pressure was seen but in this report no fetal parameters were monitored. In paper VI an increase in the umbilical blood flow of 38.5% was found after smoking. An increase in the umbilical blood flow by 25% was observed in the fetal lamb after administration of norepinephrine (Lorijn & Longo 1980). Administration of catecholamines to the pregnant ewe near term led to a reduction of the uterine arterial blood flow by approximately 40% (Rosenfeld et al 1976, Rosenfeld & West 1977). Subcutaneous injection of large doses of nicotine (0.5 to 5 mg/kg body weight) has been found to produce a reduction in uterine blood flow and intra-uterine oxygen tension in pseudopregnant rats (Hammer et al 1981). Ten min after nicotine administration, uterine perfusion was reduced by 40%. Only after a nicotine dose of 5 mg/kg did a concomitant decrease in intra-uterine oxygen tension occur. Uterine blood flow after nicotine administration has also been investigated in pregnant sheep (Resnik et al 1979, Monheit et al 1983) and in pregnant rhesus monkey (Suzuki et al 1980). In the former, a reduction of approximately 40% was recorded, with a concomitant rise in catecholamines of the same magnitude as found in humans after smoking two cigarettes (Quigley et al 1979). The response in the pregnant rhesus monkey was of the same order, with a reduction in the uterine blood flow of 38%. After nicotine infusion in the mother, acidemia and hypoxemia were observed in the fetus; the dose, however, was 10 to 20 times higher than the amount absorbed after the smoking of one standard cigarette (Armitage et al 1975). The minimum paralytic dose of nicotine and the approximate lethal dose for the rhesus monkey have been found to be six times as high as for the human being (Feurt et al 1958). Even when specific differences between species are considered, the amount of nicotine administered to the mother in the animal experiments was above the upper limit

of the amount absorbed after smoking one cigarette in the human. Nicotine administration in the pregnant sheep in a concentration of one-fourth that in the earlier mentioned animal studies did not affect the fetal acid-base balance or the oxygenation of the fetus (Monheit et al 1983), despite a reduction in the uterine arterial blood flow by as much as 42%. In the pregnant ewe the oxygen uptake of the uteroplacental and fetal tissues was not altered even by considerable changes in uterine blood flow (Clapp 1978). Likewise, the rate of umbilical blood flow varied widely without any significant change in fetal oxygen uptake. The reciprocal relationship observed in the fetal lamb between flow rate and oxygen content difference across the umbilical circulation indicates that the efficiency of oxygen extraction by tissue is constant over a wide range of flow rates (Clapp 1978). Moreover, continuous systemic infusion of epinephrine producing a decrease in uterine blood flow of 42% did not results in a concomitant decrease in uterine oxygen uptake (Clapp 1979). The increased efficiency of oxygen extraction observed at lower rates of flow may have several components. First, an increase in PCO_2 will cause a shift in the oxygen dissociation curve to the right, which will result in an increased extraction in the tissues of oxygen from the blood. Second, there may be a change in the perfusion ratio between uterine and umbilical cotyledonary flow when uterine flow is decreased (Clapp 1979). Third, tissue exposure time to capillary blood should be increased at lower flow rates. It has been stated that a reduction in the uterine perfusion by some 40-50% for one hour is well tolerated by the fetal lamb (Clapp 1979). This might be due to the constant fetal oxygenation after nicotine administration (found by Monheit et al 1983). Similarly, during acute hypoxia in the fetal lamb an increase in the umbilical blood flow by 20-40% was found (Cohn et al 1974) indicating that during hypoxia an

increase in umbilical blood flow might also compensate for the decreased oxygen tension.

Earlier, a linear correlation has been found between aortic pressure and umbilical blood flow, and between FHR and umbilical blood flow (Rudolph 1976). In papers V and VI we found an increase in FHR and even though we were not able to measure the fetal blood pressure directly, the increased aortic diameter and the enhanced maximum velocity of the aortic blood flow found after smoking gave evidence that a concomitant increase in the intravascular pressure had occurred. The increased FHR and the hypothetical increase in the mean fetal blood pressure would both lead to an increase in umbilical blood flow, in agreement with our findings in paper VI. The increase, however, was a result of an enhanced vessel diameter rather than increased mean blood velocity. The lack of an enhanced mean velocity might be due to a greater resistance in the placental circulation similar to that found in the fetal circulation after the maternal smoking. According to the equation of Poiseuille, an increased peripheral placental vascular resistance would reduce the pressure gradient, thereby diminishing the umbilical blood velocity. The dilatation of the umbilical vein found might support this theory. On the other hand, the increased FHR might tend to increase the umbilical blood velocity, thus resulting in a steady state, as was actually found in paper VI.

Conclusion

Following maternal smoking, an increase was found in both maternal heart rate (papers V, VI) and maternal blood pressure (paper VI). Parallel to the increase in fetal heart rate found in both papers, the diameter pulse curve changed typically with an increase in the velocity of the systolic part of the pulse curve. This, in accordance with the concomitant increase in amplitude of the pulsations

and the increase in aortic and umbilical blood flow, suggests and increased myocardial contractility and an enhanced cardiac output (papers V, VI). The findings of an increased diastolic diameter, together with a decreased velocity of the descending slope of the pulse curve points to an increased intravascular mean pressure. The present findings show that maternal smoking induces acute circulatory changes in the fetus similar to those found in adults. Furthermore, the studies (papers V, VI) demonstrate the feasibility of the methods to evaluate non-invasively the immediate effects of a given stress stimulus on the cardiovascular system of the human fetus.

GENERAL SUMMARY AND CONCLUSIONS

The main objective has been to survey the immediate effects of maternal smoking on certain fetal functional systems. In conjunction with this objective, which needed non-invasive ultrasonic measurement methods, the study included testing and utilization of a new method for monitoring of vessel pulsations.

Blood samples were taken to ensure that the women had abstained from smoking and to measure the strength of the stimulus (papers III, IV, V, VI). The COHb percentage was found to be positively correlated with the daily cigarette consumption (paper III). The findings of a higher mean fetal heart rate in heavy smokers than in light smokers suggest a protracted effect of smoking on the regulation of fetal heart beat intervals. In paper III, the increased breathing rate and number of apneic epochs were both correlated to maternal nicotine levels, suggesting an acute influence on the fetal behavioural state. On the other hand, no correlations were found between the nicotine concentration and the parameters of diameter pulse wave and flow rate in both aorta and umbilical vein. Other components than nicotine in the tobacco smoke might

therefore also be responsible for the acute influence of the fetal cardiovascular system.

A newly developed phase-locking ultrasound system for diameter pulse wave recording was tested in vitro (paper I) and in vivo (paper II) to establish the accuracy and the precision of the recordings. At a repetition rate of 2.56 kHz, a maximum tracking velocity of the echo complex of 438 mm/sec was found in the 10-cm dept. The minimal detectable movement was found to be 50 μm. The results obtained with the phase-locking system were closely correlated (r=0.99) to the results obtained simultaneously with an independent optical method. The potential sources of error were found to be kept to a minimum during continuous visualization on the B-mode scanner screen. The method is non-invasive and was found to lend itself especially well to measuring pulse waves in the aorta of the human fetus.

The pulsatile movements of the descending aorta (paper II) were characterized in the third trimester of normal gestation. The complexity of the diameter pulse curves was realized, and analysis was therefore based on already accepted parameters in clinical physiology. The diastolic diameter and the pulse wave velocity along the aorta increased linearly with gestational age. The diastolic diameter increased from a mean of 3.2 mm to 6.6 during the third trimester and the pulse wave velocity rose from 1.39 to 2.31 m/sec during the same period. The length of the previous beat interval was found to exert a profound influence on the pulse wave curve. Furthermore, evidence was produced that the Frank-Starling relationship was found valid also in the human fetus. Moreover, the pulse amplitude, the maximum increment velocity, and the late decremental velocity were found to be sensitive parameters in monitoring the dynamic condition of the cardiovascular system of the fetus (papers II, V).

The acute effects of maternal smoking on the FBM and the FM were determined during steady state experimental conditions (paper III). After smoking, a significant increase in the rate of FBM appeared during periods of continuous breathing, together with a reduction in the short time variability of the breath-to-breath intervals. Moreover, a clustering of the FBM and the FM after smoking was observed. These observations suggest an immediate effect of maternal smoking on the fetal behavioural state.

The acute effects of maternal smoking on the fetal heart beat intervals and their variation was analysed (paper IV). The mean beat intervals, their long-term variation (SD) and short-term variation (SDID) showed a steady state before smoking. After smoking, an 11% increase in fetal heart rate and a 17% decrease in short-term variability were found. The cardiotocograms, simultaneously recorded, showed no conventional signs of fetal compromise, however.

Two studies (papers V, VI) demonstrated the feasibility of the methods to evaluate non-invasively the acute effects of an intervention activating the adrenergic nerve system on the circulatory system of the human fetus. Smoking was found to increase fetal heart rate in all the cases in this investigation (papers IV, V, VI). The diameter pulse curve (paper V) changed typically 3 to 25 min after smoking, with an increase in the velocity of the ascending slope and an increase in the amplitude of the pulsations. This, together with the enhanced blood flow in the aorta of 21% and in the umbilical vein of 38.5% during the first 25 min after smoking, suggests an increased myocardial contractility and an increased stroke volume. Indirect evidence of an enhanced intravascular pulse pressure in the fetal circulation was found. It appears that smoking induces similar changes in the fetal circulation to those found in adults.

The observed acute effects of maternal smoking of one cigarette on the FBM, the FM and the fetal circulation are all transient, having a duration of less than 20-25 min. This implies that the influence of smoking on fetal behaviour easily can be avoided in clinical test situations by stipulating an adequate period of abstinence. The observed reaction of an increased fetal heart rate in response to maternal smoking could be of use in an attempt to dissuade pregnant women from smoking. By placing a Doppler microphone on the maternal abdomen above the fetal heart during smoking one cigarette, the increase in the fetal heart rate might convince her about the effect on her fetus.

For practical reasons the phase-locking system and the pulsed Doppler method, both combined with the real-time ultrasound technique may be useful in testing the physiological or pathophysiological responses of pharmacological agents for use in obstetrical practice. Moreover, the techniques would seem to be of value in measuring the resistance of the peripheral and the placental circulation, respectively.

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PULSE WAVE RECORDING - DEVELOPMENT OF A METHOD FOR INVESTIGATING FETAL CIRCULATION IN UTERO

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ABSTRACT

The need to investigate the elastic properties of arterial vessels *in situ* for the early recognition of degenerative disorders in arteries has long been apparent. Volume pulses in defined segments of arteries can be evaluated for this purpose and the present paper contains a survey of earlier attempts to quantify volume pulses by means of ultrasound. A presentation is given of a recently developed digital system, comprising a phase-locked echo tracker, capable of monitoring non-invasively the diameter and its pulsatile changes of a selected artery along two chosen image lines of a linear array ultrasound scanner. The physical limitations of tracking fast-moving ultrasound echoes by means of phase-locked range gating are reported and the advantage is emphasized of using a gate length of one full period. This system has been calibrated, tested and applied in measurements of pulse wave pattern and propagation velocity in the descending aorta of human fetuses in the last trimester of gestation. The present high-resolution echo-tracking method has yielded reproducible results in the fetus and appears suitable also for screening studies on adult vessels.

INTRODUCTION

The increasing incidence of disablement and death as a result of cardiovascular disease has stimulated numerous investigations into the nature and progress of degenerative diseases of the heart and the blood vessels. A high percentage of all cardiovascular disorders is associated with increasing rigidity of the arterial walls due to arteriosclerosis. It was early recognized that the elasticity of an artery is related to the velocity of volume pulse waves propagated through it (1). At the end of the nineteenth century, Moens (2) derived a mathematical expression for the velocity of the front of a pulse wave travelling along an artery as a function of inter alia the elasticity coefficient (E), the thickness of the arterial wall (a), and the end-diastolic diameter of the lumen of the vessel (d). Moens proved the validity of his formula by experiments on elastic tubings. Through the following years much effort was accomplished to define the characteristics of normal and abnormal arterial pulse waves in the human cardiovascular system, as compliance and various elastic moduli are known to differ with respect to age, anatomical location and disease. The lateral pulsations in the large arterial vessels are reflecting the pulsatile intravascular pressure and, thereby, the stroke volume output of the heart and the compliance of the vessel walls (3). A raised mean arterial blood pressure (4) and contraction of the vascular smooth musculature (5) were found to increase the propagation velocity of the pulse waves in the particular vessel. Quantitative data of volume pulse waves therefore contain substantial information on the cardiovascular function, and it is of both scientific and clinical importance to non-invasively monitor these pulses in various parts of the body. It was claimed in 1934 (1) that "for practical purposes Moens's expression is of little value, as the factors E, a, d are immeasureable quantities in situ". The aim of this paper

is to present evidence for that such a negative attitude is no longer correct. Using newly developed diagnostic ultrasound equipment it is now possible to measure the pulsatile calibre of arteries, also deeply located ones, and in the near future continuous, non-invasive monitoring of regional elastic properties in any segment of human arteries will be available. The ultrasonic system described here has initially been developed for antenatal measurements because of the need to obtain objective data from the circulation of the human fetus, where direct measurements are not possible. Furthermore, the fetus presents superior physical prerequisites for ultrasound examination thereby facilitating the application of a new investigational method.

HISTORICAL BACKGROUND

Diagnostic ultrasound is presently one of the most useful diagnostic tools in medicine. The rapid technical evolution has resulted in a string of increasingly sophisticated ultrasound equipment, often producing data of more than one diagnostic parameter simultaneously. Bom and Hugenholtz (6) have listed parameters suitable for combined sonic measurement: structure tomography, blood velocity, tissue characteristics and structure motion. In the present study we have emphasized monitoring of movements and simultaneous visualization of moving structures in the body, thereby increasing the recognition of such structures, thanks to the image processing capacity of the eye/ brain system of the human operator.

Edler and Hertz (7) were the first to utilize in medical diagnosis pulsed ultrasound in studying the motion of tissue structures, when they developed the time motion (M-mode) display. Using this one-dimensional system they described for the first time most of the presently known echo patterns in echocardiography. Continuous dynamic

measurement of organ size in conscious animals became possible with the sonomicrometer (8). This instrument determines the distance across an organ by repeated measurements of the transit time of bursts of ultrasonic energy, propagating between two transducer crystals installed on the organ walls.

An ultrasonic technique for measuring pulse waves in superficial arteries was developed for the carotid artery *in situ* by Buschmann (9) using combined A- and M-mode and later applied in studying the pressure-diameter relationship of the intact human common carotid artery by Arndt *et al*. (10). The latter investigators demonstrated that the pulsatile changes of the diameter of the undisturbed carotid artery was about ten times larger than had previously been reported from experiments on exposed carotid arteries. As a consequence of these observations, some earlier mathematical treatment of pulsatile blood flow, based upon the assumption that the pulsatile excursions of arterial walls were negligable, had to be reevaluated (11). The first ultrasonic recording of pulses of the femoral artery was presented by Hokansson *et al*. in 1970 (12) using a new echo-tracking system for recording vessel wall motion *in vivo*, and an improved system, including a phase-locked echo tracking circuit, was developed in 1972 (13). This method revolutionized the concept of echo movement detection in diagnostic ultrasound by improving the axial resolution about two orders of magnitude down to a few microns. Instead of using earlier threshold type detectors, which are inherently sensitive to the amplitude of the returning echo signals, Hokansson and co-workers adapted the automatic range tracking concept well known from radar technology (14, 15). Tracking in range could thus be achieved by applying the receiver output to two gated amplifiers, having their inputs connected in parallel. The two amplifier-gates were adjusted in timing to give a slight overlap. The difference in output of the

gates then stands for an error signal, which could be used to readjust the range of the gates to make their overlap to correspond with a time delay representing the exact range of the target. In 1976, White and Stevenson (16) used the same system for studying the pulsatile motion of intracranial echoes.

Another technical achievement, which came to influence the development of new diagnostic ultrasound equipment, was the introduction of 2-dimensional real-time scanners. The first sequences of 2-dimensional cardiac images, where structure motion could be followed, were published in Lund in 1967 by Åsberg (17) and Hertz (18). The early ultrasound scanners were mechanical, later various forms of electronic ultrasound scanners have also been developed. For our purposes the linear array scanner (multiscan) introduced by Bom et al. (19) proved to be of special interest.

The discovery of fetal breathing movements (FBM) in utero unexpectedly came to serve as an incentive for the development of instruments subsequently utilized for vascular research measurements. The existence of FBM in man was documented with simple physical equipment in the second part of the 19th century by Ahlfeld (20). The full significance of this observation and later similar reports was not recognized until 1970, when Dawes et al. (21) in Oxford and Tchobroutsky et al. (22) in Paris published their already classical works on breathing movements in fetal lambs. An extension of these studies into the human fetus was soon performed using a single-beam A-mode ultrasound reflectoscope (23), but later experience showed that recordings of FBM with A-mode ultrasound often were impaired by various artefacts, which caused misinterpretation of the signals. The influence of such artefacts was reduced with the introduction of the differential echo fetoscope (DEFS) by Maršál et al. in 1976 (24). The real

technical breakthrough, however, came with the development of the Time-Distance-recorder (TD-recorder, German patent 2644723) (25), a device for measuring, as a function of time, the relative movements of two echoes visualized by a 2-dimensional real-time ultrasound scanner. Especially for objects located deep inside the body, the 2-dimensional real-time presentation enabled correct insonation of the target and facilitated identification of the received ultrasound echoes. The TD-recorder was designed to have an axial resolution of 0.2 mm and was originally developed for recording FBM but it was also successfully utilized for registration of fetal aorta wall motion (26).

The technology of recording FBM was further elaborated in an ultrasonic imaging and differential measurement system developed by Korba et al. in 1979 (27). They combined the TD-recorder concept (25) with the phase-locked echo tracking (13) in order to obtain improved performance especially regarding the axial resolution. Although the instrument was used primarily for FBM studies, they reported also a recording of carotid arterial diameter changes in an adult. The principal disadvantage with the otherwise excellent phase-locked echo tracking is an inherent limitation of the maximum tracking velocity, which can be stated: high lateral resolution by high ultrasound frequency is incompatible with high tracking velocity. Korba et al. (27) as well as Hokansson et al. (13) used an analog equipment which limited the maximum tracking movement in one repetition period to be less than a quarter of a wavelength. A similar but digital system was published by Rapoport and Cousin in 1979 (28). By introducing a new digital measurement principle, the one-period tracking gate width, Gennser et al. in 1981 (29) were able to double the attainable tracking velocity to half a wavelength in one repetition period. (See Construction). Recent publications discussing digital methods for tracking moving interfaces include one by Rapoport and Cousins

(30) describing an instrument which is capable of simultaneously tracking up to six separate echo complexes selected on a real-time B-scan image of the fetus, and one by Groves et al. (31), who have interfaced their system with a microcomputer, where the movements of individual interfaces as well as changes between them can be calculated.

Registration of arterial wall-motion in the central vessels of the fetus might reveal important information on the dynamic output of the fetal heart and the condition of the fetal circulation either when recorded separately, or when measured concomitantly with blood flow velocity in the same vessel. For this purpose a tailor-made ultrasound equipment for measurement of the absolute vessel diameter and the pulsatile diameter changes along two selected lines in the ultrasound image was developed and is reported here in some detail. The system has mainly been used for recording instantaneous diameter pulsations in the descending aorta of the human fetus in utero, but the system is also provided with a wider measuring capacity in order to increase the field of application, e.g. to record segmental pulse wave velocity in human adult arteries.

CONSTRUCTION

The instrument for pulse wave recording is based on the TD-recorder concept (25) and designed to be adapted as an interface to any real-time linear array ultrasound scanner. At present, our pulse wave recordings are performed using an ADR (Tempe, Arizona) scanner with a 3 MHz linear array transducer. The most suitable section of a vessel selected for measurement can easily be found by adjusting the direction of the ultrasound transducer, while observing the scanner display. The pulse wave recording instrument enables the measurement of the movements of one or two echoes within the two-dimensional real-time image. The operator picks the most convenient image line for measurement and the echoes to be recorded are selected by positioning echo markers at appropriate sites. The distance between the echoes, e.g. the diameter of the fetal aorta, is measured electronically, producing an output signal proportional to this distance. The measured distance is simultaneously visualized on the ultrasound scanner screen by increasing the intensity of the line between the two selected echoes. The pulse wave recorder can display the absolute value or the relative changes of the distance between the chosen echoes.

The choice of principle for echo-tracking implies an important decision for every user of the TD-recorder:

A) amplitude threshold echo detection, where the time (distance) to a particular echo within the gate is tracked as long as the amplitude of the echo exceeds a pre-set value (29).

B) phase-locked echo tracking, as designed by Hokansson et al. (13), which locks to the zero-crossing of a single echo pulse and which is virtually independent of the echo amplitude.

The two echo-detecting systems have specific pros and cons, which are summarized in Table I. In order to make the equipment as universal as possible (for recording in the fetus e.g. FBM, other movements, pulse waves) and to benefit from the advantages of both range-gating systems, a hybrid equipment was developed. It includes one TD-recorder with amplitude threshold echo detection, and one with phase-locked echo detection. Both recorders are provided with double gates for differential measurement of distances.

	ADVANTAGE	DISADVANTAGE
AMPLITUDE THRESHOLD TRACKING	INDEPENDENCE OF ULTRASOUND FREQUENCY ● HIGH TRACKING VELOCITY ● DEFINES EDGE OF ECHO COMPLEX	AMPLITUDE DEPENDENCE ● LOWER RESOLUTION ● INABILITY TO LOCK WITHIN ECHO COMPLEX
PHASE-LOCKED TRACKING	EXTREME RESOLUTION ● AMPLITUDE INDEPENDENCE ● ABILITY TO LOCK WITHIN ECHO COMPLEX	LIMITED TRACKING VELOCITY ● HIGH LATERAL RESOLUTION INCOMPATIBLE WITH HIGH TRACKING VELOCITY

Table 1. Evaluation of the two range-gating detector systems.

As appears in Table I, the phase-locked echo detection has a high spatial resolution, which is excellent for pulse wave recording but has limited tracking velocity. This apparent paradox is elaborated in the following. The function of the phase-locked echo detection used by Korba et al. (27), as shown in Fig 1A, can be examined as an example. A feedback loop maintains the time of occurrence of a gate eclipsing symmetrically a zero-crossing of the selected ultrasonic echo. To the left in the figure, the situation is shown, when an echo is produced by a stationary structure. The position of the gate is symmetrical around the zero-crossing, which results in zero output from the integrator. If, however, the structure has moved closer to the transducer, causing the echo to occur at a slightly earlier time, the integrator output will be a negative voltage (see right part of Fig 1A). This voltage is used to move the gate somewhat towards the transducer, so that it again symmetrically eclipses the zero-crossing of the next echo pulse (provided that there has been no subsequent movement). However, if the echo has moved more than a quarter of a wave-length between each measurement, the phase-locked echo detector is uncoupled and might lock at another zero-crossing. This results in a measuring error amounting to a minimum half a wavelength. Such a situation is evident in Fig. 1B, which shows the output signal from the integrator as a function of the echo movement between each measurement. The figure demonstrates that the integrator output is linear only within range $\pm \lambda/4$. Beyond this range the signal will again be reduced and is zero at $\pm \lambda/2$. This implies that the phase-locked echo detector can directly compensate for echo movements up to a quarter of a wavelength. For echo movements between $\lambda/4$ and $\lambda/2$, the situation is more complex. If the echo movement occurs in one single step, the phase-locked echo detector will successively move in the right direc-

tion and finally lock again in the correct position. If the echo moves continuously, the detector will face a

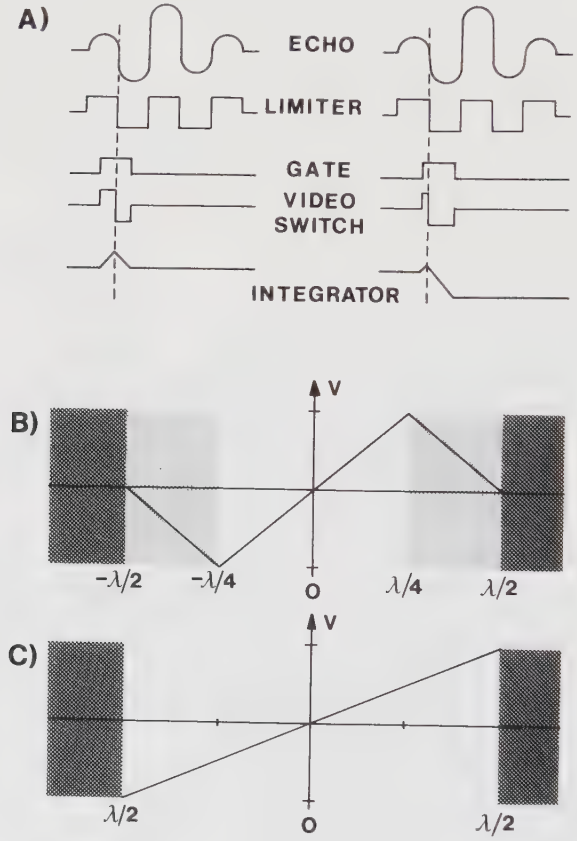

Fig 1 A/ Principle of the phase-locked detector.
B/ Integrator output signal (ordinate) as a function of the echo movement (abscissa) for the phase-locked detector ad modum Hokansson et al. (1972). Echo movements beyond $\lambda/4$ result in non-linear operation. Dependent on the type of movement, the detector might lock also in the range $\lambda/4$ - $\lambda/2$. Echo movements > $\lambda/2$ will always result in signal escape.

C/ Corresponding diagram for the phase-locked detector ad modum Gennser et al. 1981. This detector has a linear operational range within $\pm \lambda/2$.

large risk to go out of locking and find another zero-crossing in the echo complex to lock on to. For echo movements larger than $\lambda/2$, the detector will immediately lock on another zero-crossing. In order to maintain the phase-locked loop in lock, it is necessary to measure sufficiently often, thus enabling the maximum target movement in one repetition period to be less than $\lambda/4$.

This limitation of the maximum tracking velocity, existing as a natural quality of the phase-locking echo detection principle, is, however, possible to partly overcome. One solution was described by Gennser et al. (29), and a corresponding "integrator output versus echo-movement" graph relating to this phase-locking system is shown in Fig. 1C. It appears that using this method we can directly restore echo-movements of up to $\lambda/2$, which is twice the performance of earlier phase-lock systems. For larger echo deviations ($> \lambda/2$), the gate will uncouple and find another zero-crossing to lock on to. The trick with this detector philosophy is to utilize a gate length of one full period, which easily can be implemented in the digital version shown in Fig. 2.

Fig. 2A, which can be compared to Fig. 1A left, shows the function of the phase-locked detector, when the echo arises from a stationary structure and the gate is symmetrical to the selected zero-crossing. Fig. 2B demonstrates the situation, when the structure has moved closer to the transducer. In this case, the negative flank zero-crossing will arrive before the "middle of gate"-pulse and during this interval a gate will open and let pulses from the master clock reach the "down-counter". The position of the

gate will be adjusted closer to the transducer in accordance to the number of clock pulses, which are let through. Analogously, if the echo has moved away from the transducer, another gate will open and let pulses to the "up counter", which in turn will move the gate away from the transducer making it again symmetrically eclipse the selected zero-crossing of the echo.

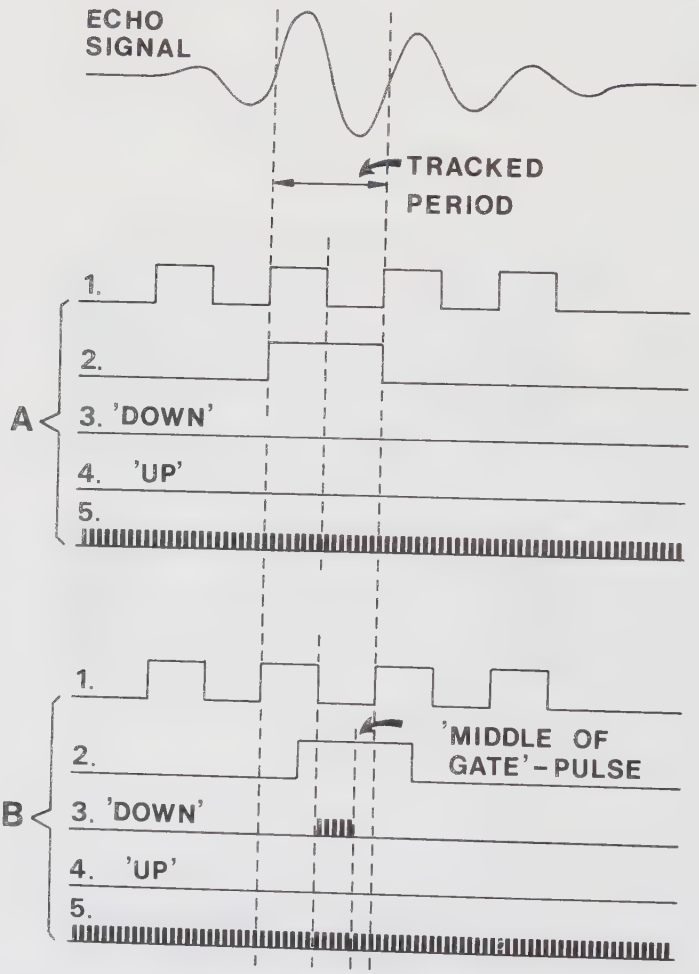

Fig 2 Sequence function diagram of a TD-recorder with digital range tracking (phase-locked loop system). 1. Comparated echo signal, 2. Gate,

3. Clock "down", 4. Clock "up", 5. Master clock.

A/ The gate is aligned with the echo. No clock "up" or clock "down" pulse.

B/ The echo has moved with respect to the gate pulse. The "down" pulses are repositioning the gate pulse in relation to the echo signal.

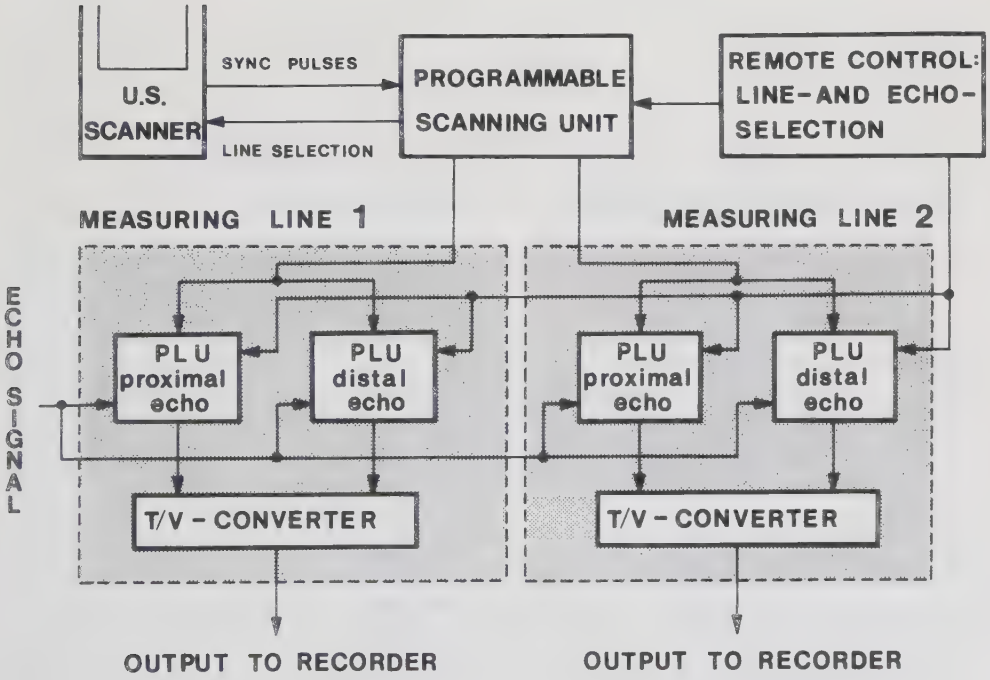

Fig 3 Block diagram of the phase-locked echo tracker, dedicated to pulse wave recording.

In most of the pulse wave recordings produced so far, we have used the instrument described here. However, as a consequence of the clinical experience gained, we have recently concluded the construction of a new, dedicated

pulse wave velocity recorder, as shown in Fig. 3. This specialized interface is micro-computer controlled and contains two complete, independent sets of double phase-locked echo detection units (PLU) (29). With this instrument it is possible to measure simultaneously the pulsatile differential movements of the arterial walls at two selected sites, A_1 and A_2, at a mutual distance d (Fig.

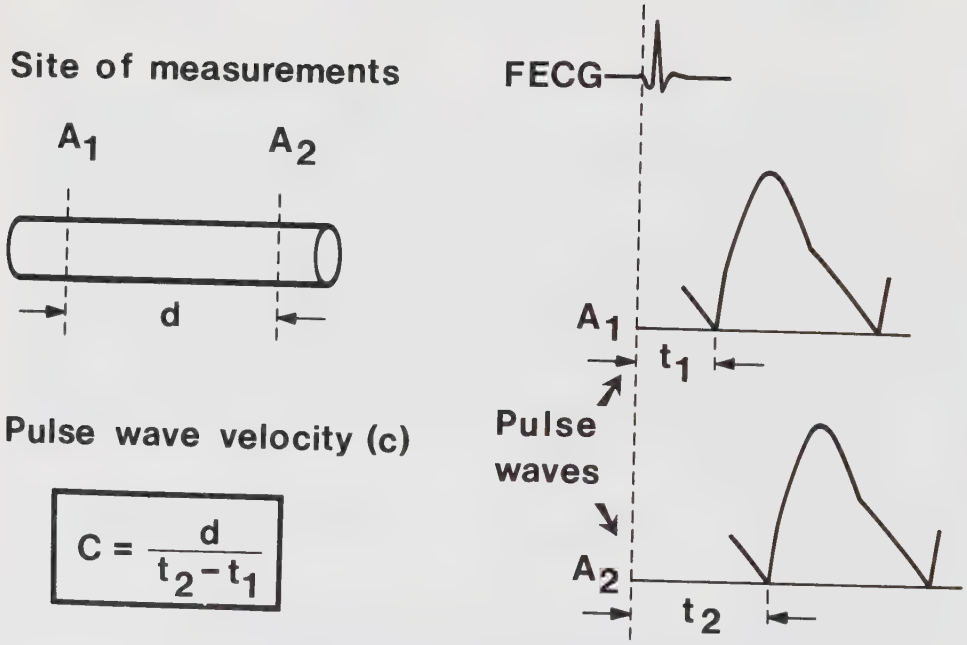

Fig 4 The principle for measuring of pulse wave velocity. The same set up can be used for detailed study of pulse wave pattern and changes along the vascular tree.

4). By measuring the arrival time of the pulse wave at the two measuring sites (t_1, t_2) in relation to recorded fetal electrocardiogram (FECG) or, simply, by measuring the differential time of arrival (t_2-t_1), values of the pulse wave propagation velocity (c) can easily be calculated for defined segments of the vessel. New data on the central and the peripheral circulation of the human fetus have been obtained by this method (see Application).

CALIBRATION

Measurements were performed to evaluate the accuracy of the complete phase-locked TD-recording system in vitro. The experimental procedure was similar to that described by Maršál et al. in 1978 (32) and also used by Korba et al. in 1979 (27). This procedure implies static calibration of the entire real-time B-mode system, including the ultrasonic scanner, the phase-locked TD-recorder and the polygraph recorder, using suitable stepped test blocks. Furthermore, dynamic calibration to test the accuracy of target movement as well as to assess the resolution and the maximum tracking velocity of the phase-locked TD-recorder was performed. For linearity tests and dynamic calibration was used a small, reflecting test target, immersed in water and mechanically connected to the pen holder of an X-Y-recorder, driven by a function generator. The movements of the target, using various test waveforms, frequencies and amplitudes, were detected and recorded on the polygraph to be compared with the test signals from the function generator.

An electronic echo-simulator, earlier described by Lindström and Holmer in 1978 (33), was utilized to determine the maximum tracking velocity. The minimal detectable movement of the TD-recording system was 50 microns and the maximum tracking velocity, at a penetration depth of 200 mm, was found to be approximately 220 mm/sec. If the

penetration depth was reduced to 100 mm (sufficient for most fetal recordings), the maximum tracking velocity was, as expected, increased to around 440 mm/sec.

Finally, we were interested to test the performance of the new phase-locked TD-recorder in a more realistic situation. For this purpose, we TD-recorded controlled pulse-waves along a rubber tube and simultaneously measured the instantaneous tube diameter by an independent measuring

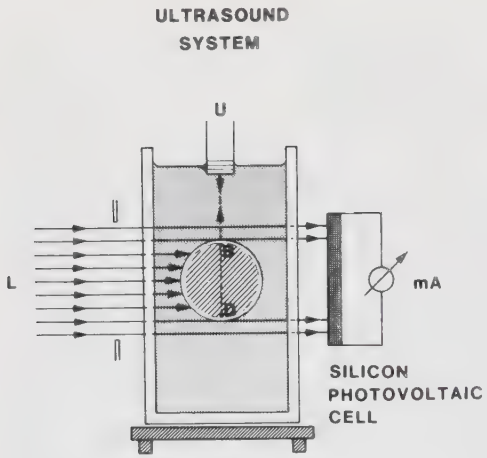

Fig 5
Set up for validation test using two independent methods for dynamic quantification of the pulsatile B-D-interval of a rubber tube immersed in oil.

modality utilizing another physical parameter. This test yields indication of the TD-recorder performance in vivo, as the received ultrasound echoes will vary in amplitude and appearance in different phases of the pulse wave. The test arrangements are shown in Fig. 5. A pulsating rubber tube, filled with dyed fluid and immersed in oil, was used as a target. The TD-recorder was installed at the top of the measuring container and the two echo-trackers were locked to echoes from the tube at B and D. The pulse waves of the tube were simultaneously measured with an optical system, recording the shadow of the opaque, dyed-filled tube. The optical system was aligned perpendicularly to

the ultrasound system to ensure that the two systems were recording the identical diameter (and to exclude possible measuring faults due to non-symmetrical diameter changes in the tube). The light-source was either a slide-projector, where the lamp was modified to DC-drift from a stabilized supply and the light screened off by means of a slit-shaped aperture, or a He-Ne laser, equipped with a light-plane lens, to produce a narrow, parallel light beam. A silicon photovoltaic cell, with an active surface sufficiently large to cover the shadow from the immersed tube, was used as photodetector. When the diameter of the

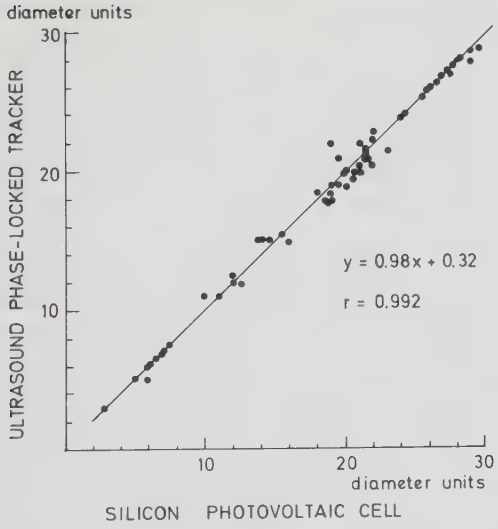

Fig 6
Correlation of data from a pulsating rubber tube obtained with the two indenddent measuring systems in Fig 5.

tube increased, the distance between B and D as measured with the TD-recorder would increase but the illuminated part of the photodetector decrease. In order to ensure linear operation, it was essential for the photovoltaic cell to work in current mode. This operation demanded that the photodetector was connected to a current operational amplifier, which simultaneously with the measuring reversed the phase of the optical signal. As shown in Fig. 6, a high degree of agreement was found in static and dynamic tests between the measurements obtained with the two systems.

THE PULSE WAVE AND ITS PHYSIOLOGICAL CORRELATE

It is pertinent to emphasize the difference which exists between various forms of pulses appearing in the circulation (which often are confounded for semantic reasons). Thus, the flow pulse and the pressure pulse differ from each other in that the latter attains its maximum later in the cycle and does not fall to zero or to negative values in diastole. The characteristics of the pressure pulse are caused by the contraction of the heart, the rectifying effect of the aortic valves, the elasticity of the arterial walls, and by the peripheral resistance. The cross-sectional or volume pulse, defined as the dilatation and the elongation of the arterial walls produced passively by the variation of the intravascular pressure (34), implies a transformation of kinetic energy of the running blood into deformation energy and a simultaneous storing of the stroke volume of blood in the aorta. During the phase of falling pressure, blood in the stretched aorta and arteries of elastic type is forced into peripheral direction by the conversion of deformation energy into kinetic one, thus changing the discontinuous flow from the heart into a continuous but not uniform flow in the peripheral arteries.

The pulse-wave velocity (PWV), i.e. the propagation of the deformation of the vessel from one site to another, is considerably higher than the velocity of blood flow. The PWV is dependent on the distensibility of the arterial wall and on the relative thickness of the vessel walls, the velocity being higher the more rigid or thicker the vessel is and the smaller the radius. The PWV in the adult aorta is 4-6 m/sec, in the radial artery 8-12 m/sec (35). The PWV is increased in high age with diminishing elasticity of the arterial walls and also in the presence of high blood pressure, when the vessel walls are more rigid due to stretching.

The shape and amplitude of the pressure pulse have been known to change markedly by increasing distance from the heart. In the aorta and in the arteries exceeding 3 mm in diameter, the systolic pressure increases progressively while the diastolic pressure decreases slightly, which gives a distinct rise in pressure amplitude. The cause of these changes is still under debate, the major factors considered being wave reflections, damping processes and PWV dependency on frequency (35). The reflections in the arterial system appear due to increased impedance at sites of vessel divisions, due to decreased elasticity in peripheral arteries, and due to increased peripheral resistance in the precapillary vessels. Such reflected waves can augment the systolic pressure by superposition on the primary wave but are considered unlikely to build up standing waves because of the high degree of damping. The damping depends on the compliance of the vessel walls and is larger when arteries divide or get smaller in peripheral direction. The damping is stronger for the higher frequencies, which partly explains the disappearance of the incisura (a notch in the curve caused by the sudden closure of the aortic valves at the end of the systole) in the lower part of the abdominal aorta of adults. Moreover, due to the increased pressure in the distal arteries, the lowered distensibility and thus the higher PWV account for the more rapid propagation of the systolic component than the diastolic component in the pulse wave, which contributes to make the wavefront steeper and increase the maximum value of the pulse wave.

The shape of the pressure pulse and its PWV is dependent on hemodynamic factors such as the cardiac stroke volume, the vessel compliance and the peripheral resistance (34, 35) and the pulse curve might thus be utilized for diagnostic purposes. The peripheral pulse is modified by the properties of the peripheral vessel walls and must therefore be distinguished from the central pulse. It has been

claimed earlier, when measuring capacity was restricted to peripheral arteries only, that "on account of the poor transmitting ability of the arterial system, the peripheral pulse reproduces only inaccurately the pressure changes established in the aorta, and consequently it may be anticipated that its diagnostic value will be correspondingly less..." (34). The direct measurement of the pulse waves at various sites of the fetal aorta with the present echo-tracking system thus creates a new situation of diagnostic possibilities in both antenatal and adult circulation.

APPLICATION

The pulse wave recording method has up to now been applied on more than 100 fetuses for measurements of pulses in the descending aorta during the last trimester of gestation. The choice of the fetal target facilitated recordings by factors promoting ultrasound transmission: the amniotic fluid surrounding the fetus, the absence of gas in the fetal lungs and intestinal canal, and the high water contents of the fetal tissues. The recordings have been performed near the diaphragm, which is an easily recognizable level of the aorta in the ultrasound image, and at further levels proximal or distal to the previous one. The distance between two recording levels was subsequently measured with the caliper of the ADR scanner in 1-mm steps and used for the calculation of PWV.

The methodological error was tested as the variance within and between observers in three patients examined by three different operators. In each patient, 10 consecutive pulse waves were recorded during steady state conditions, and each observer calculated the parameters from identical curves of the three patients. The analysis of variance was carried out by the use of an F-distribution test with 5% as the level of significance. No significant difference

was found between the variance within and between the three observers with F-values ranging from 0 to 3.33.

Provided that the fetus was in a resting state, i.e. displaying neither FBM nor gross trunk and limb movements, a satisfactory recording of pulse waves in the aorta was obtained in the major number of investigations: a continuous record of at least 10 pulse cycles was required for acceptance. Continuous recordings of long duration occasionally demonstrated a considerable variation of the pulses as with the occasional occurrence of extrasystolic beats (Fig. 7). It appears from such recordings that the

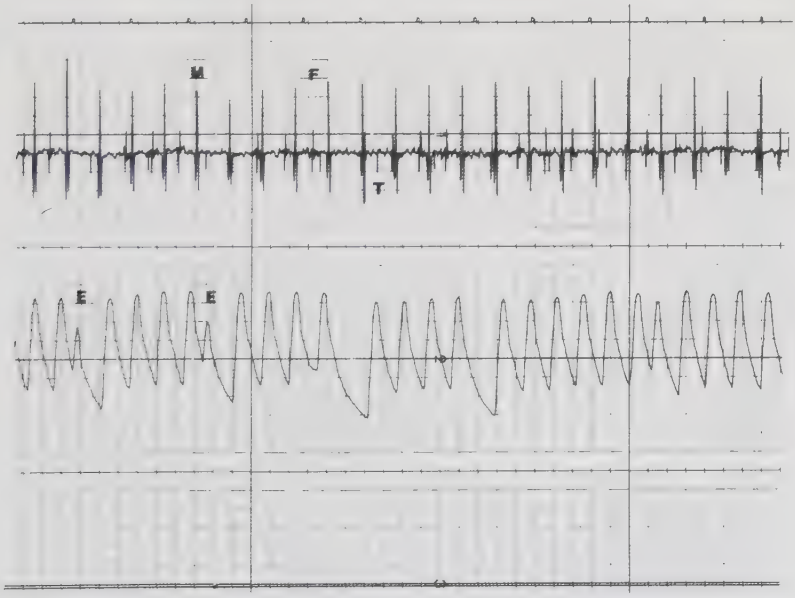

Fig 7 Example of continuous recording of the diameter in fetal descending aorta (lower trace) and simultaneously obtained fetal ECG (F, upper trace). M denotes maternal complexes, T denotes time signal. Note the occurrence in the pulse trace of cycles (E) emanating from extra-systolic beats followed by post-extra-systolic compensatory periods.

diastolic diameter of aorta depends on the time for relaxation of the vessel wall. After a short previous cycle, an extrasystolic pulse starts off from a larger vessel diameter (and thus a higher intravascular pressure) than after a normal beat; after a long compensatory pause the onset of the pulse occurs from a smaller diameter (and a lower pressure). Such pulse curves of varying duration do not merely illustrate a difference in relaxation of the vessel wall but also a changed pulsatile amplitude of the subsequent cycle, which suggests that the cardiac stroke volume is positively related to the duration of the previous beat interval and therefore to the degree of diastolic filling. These observations for the first time give evidence that also the fetal heart regulates its

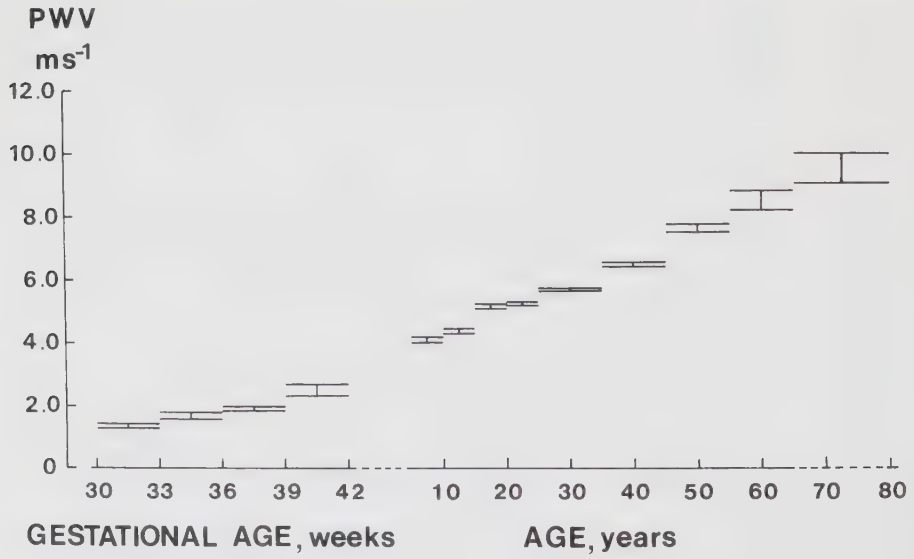

Fig 8 The pulse wave velocity in the descending aorta during the life cycle of man. The fetal values are obtained cross-sectionally from 37 fetuses in uncomplicated pregnancies; "extra-uterine" values to the right are adapted from (1). The horizontal bars denote mean $\pm$ 2SD.

activity by the end-diastolic volume according to the Frank-Starling mechanism (36), a connection which was earlier disputed (37).

With the present method has also been evaluated the range of PWV in the fetal descending aorta during the last trimester of gestation. In 37 fetuses studied cross-sectionally during uncomplicated pregnancy, a gradual increase of the PWV with gestational age was found (Fig. 8). It is noteworthy that the variability of the PWV within the ten cycles studied in each fetus seemed to increase near term suggesting a greater range of the circulatory parameters possibly due to the integration of more regulatory mechanisms with advancing maturity (38). The mean levels of PWV in the aorta was observed to be definitely lower in the late fetal period than the PWV calculated in childhood, adolescence and adult life of man from simultaneous recordings of the carotid and iliac pulses by kymographic technique (1). The latter values show a rather constant biological variation from 5 to 40 years, the subsequently appearing greater variability later in life presumably being caused by degenerative changes in the vessel walls (1).

Studies on fetal pulse wave characteristics in pathological gestation have also offered new information of interest. When the age-related values of the PWV in the descending aorta in 13 fetuses exhibiting intrauterine growth retardation were compared with those of the 37 fetuses above in uncomplicated pregnancy, the PWV exceeded the mean + 2 SD in 12 of the former group (Fig. 9). These observations suggest that in some growth-retarded fetuses the peripheral resistance to the circulation in aorta is increased and that presumably their systemic blood pressure might be raised (to be published).

Thus, the present ultrasonic, high-resolution system for non-invasive quantification of pulse waves in deep vessels has proved to yield reproducible and highly informative data on the fetal circulation. It has not escaped the authors that this system also has promising potentialities for early detection of degenerative processes in adult vessel walls.

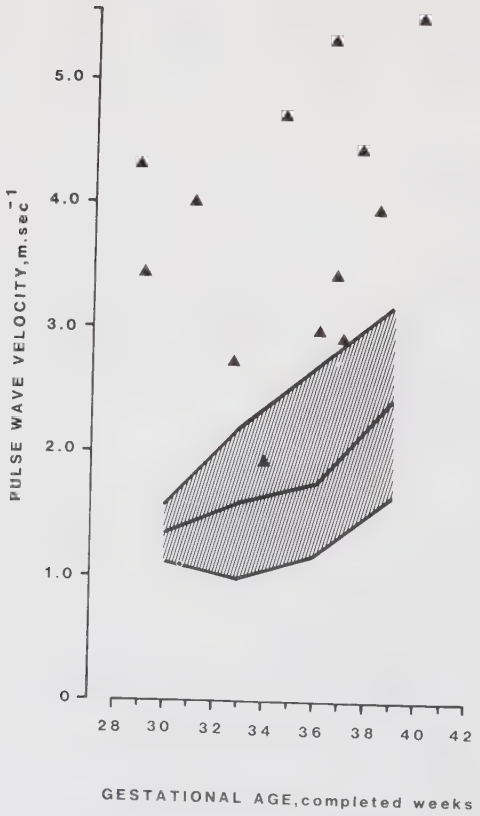

Fig 9 The pulse wave velocity in the descending aorta in 13 growth retarded fetuses in the last trimester as compared to the normal range.

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PHYSIOLOGICAL CHARACTERISTICS OF DIAMETER PULSES IN THE FETAL DESCENDING AORTA

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Abstract. A study was performed to establish the dynamic behavior *in situ* of the descending aorta in the human fetus. The pulsatile movements of the vessel walls were recorded in 36 clinically normal fetuses using a real-time phase-locked ultrasonic system measuring echo movements with high spatial and temporal resolution. The mean amplitude of the diameter pulsations was similar in the 28th–35th week to that in the 36th–40th week but, as the apparent diastolic diameter increased, the pulse-elicited increment of the cross-sectional area was 29% larger in the older group. The diastolic diameter decreased ($p < 0.001$) and the amplitude of the diameter pulsation increased ($p < 0.001$) with prolongation of the previous beat interval. The diameter pulse velocity was positively correlated to gestational age ($p < 0.001$), ranging between 1.35 and 2.89 m/sec. The incremental phase of the pulse curve diminished in duration with increasing distance from the heart ($p < 0.001$) and with decreasing duration of the previous beat interval ($p < 0.001$). The maximum slope of the incremental phase was higher in the more distal part of the aorta ($p < 0.001$). The study demonstrates that the diameter pulses contain useful information on the cardiovascular dynamics and provides evidence that the Frank-Starling mechanism is effective also in the human fetus.

Key words: Pulse wave, fetal aorta, fetal physiology, ultrasound

Recording by plethysmography of the pulsations in peripheral arteries has proved useful in adults for obtaining information on vessel compliance and peripheral resistance. The pulsatile characteristics of fetal vessels are also of considerable interest in view of recent clinical observations. Thus, Gosling and coworkers demonstrated a change in aortic compliance related to age and sex during childhood and adolescence (10), and varying compliance (4) as well as structural reconstruction (21) was found in the iliac arteries of infants born with only one umbilical artery.

Non-invasive recording of the diameter and diameter changes in vessels using pulsed ultrasound was early reported by Arndt, who monitored the pulsations of the carotid artery in adults (2). Hokanson and Strandness improved the ultrasound technique to include a phase-locked echo tracking system, thereby accomplishing a virtual independence of amplitude changes of the ultrasonic echoes (14), and their system has been used for measuring fetal movements (17). A modification of the Hokanson design for the specific purpose of recording pulsations of fetal vessels has been elaborated by the present authors (19), and tested in vitro and in animal experiments (Sindberg Eriksen et al., to be published). This report describes the basic characteristics of the pulsations in the descending aorta of the human fetus in the last trimester of normal gestation. It demonstrates the dependence of the pulse waves on biophysical variables in the circulatory system, and provides reference data for further investigations on pathological pregnancies and on the influence of maternal smoking on fetal circulation.

MATERIAL AND METHODS

Thirty-six fetuses in the 28th to 42nd week of normal gestation were studied. Their gestational ages were confirmed by early ultrasound fetometry, and their weights were routinely estimated from the sonically measured biparietal and abdominal diameters. Gestational age at birth, subsequently was 39.1±1.5 (mean±SD) weeks, and birth weight was 3 111±618 g. The mean Apgar scores at one and five minutes were 8.9 and 10.0, respectively.

Individual recordings of pulse waves were performed on 29 of the fetuses (range of gestational age 28 to 42 weeks), while 7 fetuses, in the 35th to 37th week of gestation, were examined three times on the same day (1100, 1300 and 1500 hours). The women lay recumbent, supine and tilted slightly to the left during the measuring. Only recordings with the

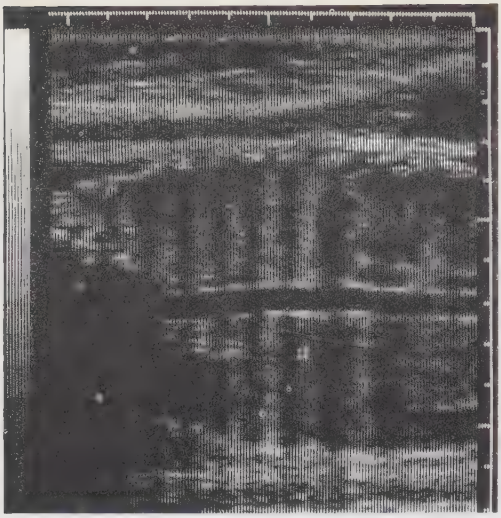

Fig. 1. Ultrasonic longitudinal section of descending aorta in a human fetus (37th gestational age). The white marker indicates the persistent, well defined angle representing the passage of the vessel through the diaphragm.

fetus in a resting state were accepted, i.e. with no fetal gross movements and no fetal breathing movements visible on the ultrasound screen.

Pulse waves were obtained by continuous measurement of the diameter of the fetal aorta at a preselected level. An electronic echo-tracking instrument developed for this specific purpose (9) was used, connected to a real-time ultrasound scanner (ADR, Tempe, Arizona) with a linear array 3.0 MHz transducer. The new instrument (Diamove 820, Teltec, Lund, Sweden) contained two tracking gates, each of which could be synchronized with a zero-crossing of a cycle in a moving echo complex. The tracking, effected via a phase-locked loop, yielded information of the instantaneous distance between two moving echoes, thus enabling direct monitoring of the pulsatile arterial diameter. The measuring range from the transducer was optionally 10 or 20 cm; at the former distance the repetition frequency of the measurements was 2.56 KHz and the maximum tracking velocity of a moving object was 320 mm/sec. As the smallest detectable echo movement was 30 μm, the spatial resolution of echo movements considerably exceeded the resolution of static objects provided by the real-time scanner. External fetal ECG was obtained with a custom-built electrocardiograph producing recordings sufficient to define the onset of the fetal Q-waves.

The descending aorta was identified in a longitudinal ultrasound section of the fetus and the transducer was fixed in a position parallel to the course of the vessel. A line-selecting program of the echo-tracking instrument permitted a continuous survey of the target on the ultrasound screen concomitant with the measurement of the vessel diameter. To monitor the diameter pulses at a preselected level of the vessel, the electronic marker of each tracking gate was positioned over the echo image for each vessel wall. The locking was adjusted so as to occur as closely as possible to the inner surface of each wall, the distance between the walls then being measured automatically in a plane perpendicular to the longitudinal axis of the vessel. All the measurements, when not otherwise stated, were made just caudal to the diaphragm, a level easily recognizable because of a well defined notch or angle representing the passage of the aorta into the abdominal cavity (Fig. 1). To calculate the propagation velocity of the pulse wave, recordings were made in 24 fetuses both at the diaphragm and at a second level further down the abdominal aorta. The distance between the recording levels was measured on the scanner screen with the built-in calipers (1-mm steps) and the dual recordings were made within an interval of 1 – 2 min. An electronic signal calibrating the distance was inserted at short intervals between the recordings.

The fetal ECG and the output signals from the tracking instrument were stored on magnetic tape and later played back on a chart recorder with a paper speed of 200 mm/sec. A digitizer (HIPAD, Houston Instr., Houston, Texas) feeding a microcomputer was used for off-line analog-to-digital conversion of the pulse curves, and for statistical calculations. Averaged data of 10 consecutive pulse cycles were calculated in each measurement.

The following characteristics of the analog curves were calculated:

1. The *diastolic diameter* (minimum diameter at onset of pulse curve), the *systolic diameter* (maximum diameter at peak of pulse curve), and the *pulse amplitude* (ΔD, the difference between systolic and diastolic diameters), all values expressed in mm.

2. The *pattern of the pulse curve* was defined by the following parameters:
   a. The *crest time* from onset to peak of the pulse wave, expressed in msec or as a percentage of the pulse interval (27).
   b. The *inclination time*, the duration of a tangent fitted to the steeply ascending limb of the curve between its intercept with the minimum diameter and the maximum diameter, expressed in msec or as a percentage of the pulse interval (27).
   c. The *maximum increment velocity*, the slope of the steeply ascending part of the pulse wave (expressed in mm/sec). This parameter is equivalent to the rate of rise of the anacrotic limb (25).

3. *The propagation time*, the time (in msec) between the onset of the Q-wave of the fetal ECG and the onset of the pulse wave at the recording site. The major constituent of the so defined propagation time is the pre-ejection period (PEP). As the duration of the PEP has been reported to vary with the heart rate under steady conditions, the values of propagation time obtained were corrected for the varying heart beat intervals, using data supplied by Organ et al. (22).

4. The *pulse wave velocity* (m/sec) was calculated as the difference between the propagation times to two different recording levels divided by the distance between these levels.

Statistics

Statistical analyses included *t*-statistics for paired and unpaired observations, and rank sum test for unpaired data. To calculate the correlation coefficients we used either the overall mean value per fetus of the parameter studied (versus gestational age), or the mean value for each recording (versus distance from the heart) or the value of individual measurements (versus heart beat intervals).

RESULTS

Basic data

The pattern of the diameter pulse curve recorded from the fetal aorta at diaphragm level was consistent during regular heart rate. The initial phase of the upstroke was rapid, while the latter part of the systolic portion was dome-shaped. No clear-cut notch reflecting the closure of the aortic valves was visible in the descending leg of the curve, but in 68% of the curves an angle appeared between the rapid initial downstroke and the subsequent, less sloping part. This angle was found at an average of 48% of the pulse amplitude above the diastolic level.

Diastolic diameter

The diastolic diameter of the aorta was measured in 24 fetuses (the system was not calibrated absolutely during the first 12 patients who only had ΔD measured) and averaged 5.4±1.0 (mean±SD) mm. This diameter was found to depend on the *gestational age* (Table I); within the gestational period studied, it increased linearly with age ($y = 0.28x - 4.60$; $r = 0.89$, $p < 0.001$) (Fig. 2).

The diastolic diameter was also related to the duration of the *previous pulse*: the longer the cycle, the smaller the diastolic diameter (for an example, see Fig. 3). In one fetus (M. C.) with a highly variable heart rate, there was a negative correlation in 75 pulse curves between the diastolic diameter and the pre-

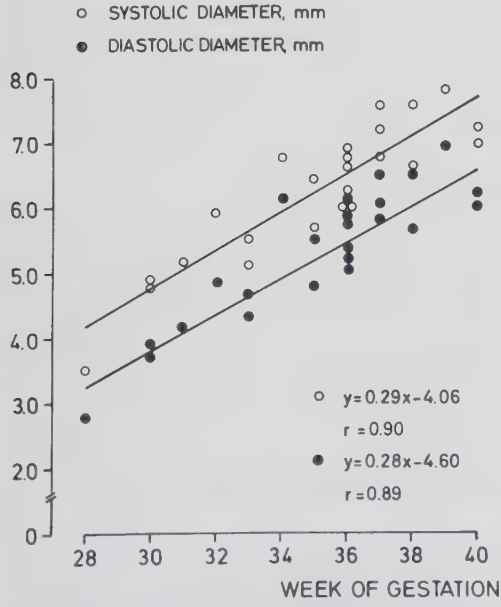

Fig. 2. Systolic and diastolic diameters of descending aorta from 24 fetuses of 28th – 40th week of gestation. Each symbol represents the mean of 10 consecutive diameter pulses.

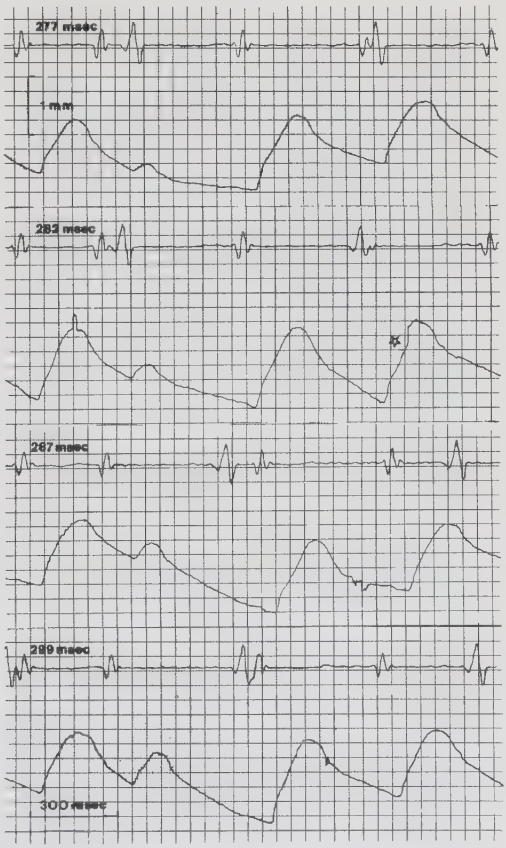

Fig. 3. Four recordings of fetal heart beats, each containing one extrasystolic beat starting at increasing interval from the preceding beat (inserted time figures). Upper trace denotes abdominal ECG with maternal and fetal complexes; lower trace shows the diameter pulse wave of the fetal aorta.

Asterisk indicates a jump in the diameter trace due to an artefactual move of the echo tracker of ½ wavelength.

Table I. *Basic data of fetal aorta descendens in two periods of the third trimester.*

	Gestational age (weeks)	Diastolic diameter (mm)	Pulse amplitude (mm)	Pulse amplitude (per cent of diastolic diameter)	Pulsatile area change (mm^2)
Median	33	4.32	0.90	22.0	7.36
Range	28 – 35	2.81 – 5.53	0.70 – 1.09	28.9 – 14.9	3.49 – 9.30
N = 10					
Median	37	6.02**	0.97	16.0**	9.52**
Range	36 – 40	5.10 – 6.94	0.73 – 1.14	20.4 – 12.7	6.63 – 12.30
N = 14					

**$p<0.01$, rank sum test for unpaired data

vious pulse interval ($y = -0.01x + 11.57$, $r = -0.56$, $p<0.001$) and a similar correlation was found in the other fetuses with a less variable heart rate. On the other hand, there was no correlation between the systolic diameter and the previous pulse interval. It was generally observed that in steady-state sequences of pulse intervals, i.e. with extrasystolic cycles excluded, the systolic diameter was more stable than the diastolic diameter.

Pulse amplitude (ΔD)

The average amplitude of the pulsations (ΔD) did not change significantly between the 28th – 35th week and 36th – 40th week (Table I). As the diastolic calibre of the vessel increased between these gestational periods, the pulsatile area increments (calculated for a circular vessel section) increased by 29% between these two periods. However, there was no change with gestational age, when the pulsatile area increments were expressed relative to the estimated fetal weight, i.e., 3.75 $mm^2 \times kg^{-1}$ for the whole period studied.

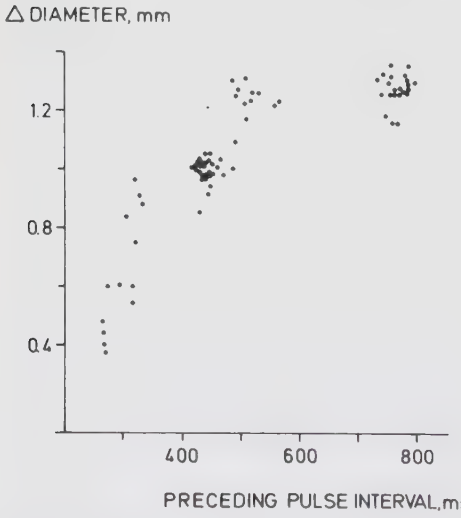

Fig. 4. Amplitude of 75 pulse waves recorded in descending aorta and plotted against preceding pulse interval. From a fetus (M. C.) of 33 weeks gestational age with episodes of extrasystole and bradycardia.

The ΔD of the individual fetus was observed not to vary with the distance from the diaphragm in the abdominal aorta. On the other hand, the ΔD increased with the lengthening of the preceding pulse interval. When data were pooled from 10 fetuses showing a considerable variation in pulse intervals within the physiological range, the ΔD was positively correlated to the preceding pulse interval ($y = 0.214 + 0.018x$; $r = 0.76$, $p<0.001$). Beyond the physiological range of heart rate this relationship was asymptotic, as illustrated by data from a fetus (M. C.) with beat intervals ranging between 260 and 790 msec due to extrasystolic beats and periods of bradycardia (Fig. 4).

Propagation time and velocity

The time (including the PEP) for propagation of the pulse wave down to the fetal diaphragm was significantly longer when the preceding pulse interval was 400 msec, than when the interval ranged between 700 and 800 msec (Fig. 5). The propagation velocity calculated over a measured segment of the abdominal aorta below diaphragm level ranged from 1.35 to 2.89 m/sec (Table II) and was positively correlated to the gestational age ($y = 0.10x - 1.86$; $r = 0.69$, $p<0.001$). The length of the preceding pulse interval did not significantly influence the propagation velocity.

Analysis of pulse wave shape

The relative *crest time* in the entire group of measurements comprised 26.6±1.7 % of the pulse duration. During the passage of the pulse wave along the abdominal aorta, the crest time decreased with increasing

Table II. *Pulse wave velocity in fetal aorta descendens.*

Weeks of gestation	Pulse wave velocity, m/sec		No. of patients	No. of recordings
	Mean	Range		
30	1.39	1.35–1.43	1	2
32	1.30	1.19–1.40	1	2
33	1.43	1.21–1.75	3	3
35	1.79	1.54–2.46	4	16
36	1.74	1.29–2.15	5	20
37	2.04	1.52–2.80	6	22
38	1.52	1.48–1.56	1	2
39	2.34	1.69–2.93	2	6
42	2.31	1.72–2.89	1	2
Total			24	75

Calculation of pulse wave velocity in 24 normal fetuses between 30 and 42 weeks of gestation. The values are based on measurements of 20 pulse waves at two different points in each recording

distance from the heart (Table III). No correlation of crest time to gestational age was found. A significant positive linear correlation appeared in 24 fetuses between mean crest time and the duration of the preceding pulse ($y = 0.24x + 12.04$; $r = 0.76$; $p < 0.001$), when the fetal heart rate was within the physiological range. When the heart beat interval exceeded this range, the data points in one fetus (M. C.) with extrasystolic beats and bradycardia showed an exponential curve fit ($y = 151.5\ (1 - e^{-0.003x})$; $r^2 = 0.56$, $n = 65$). For large pulse duration values, the crest time values converged towards a value of 151 msec.

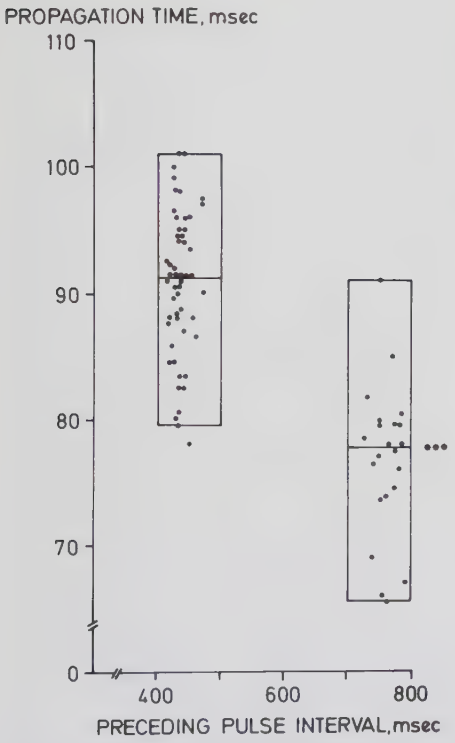

Fig. 5. Propagation time of diameter pulse wave along the thoracic aorta in two groups of heart cycles, with preceding pulse intervals ranging 400–500 msec, and 700–800 msec, respectively. Horizontal bars indicate median, 2.5 percentile and 97.5 percentile, respectively. ***$p < 0.001$.

The *inclination time* was 10.6±1.3% of the pulse length and was subject to changes similar to the crest time in response to alterations of the distance from the heart (Table III). It did not change with gestational age, but was positively correlated to the preceding pulse length ($y = 0.13x - 9.64$; $r = 0.65$, $p < 0.001$).

When measured at diaphragm level, the *maximum increment velocity* of the diameter pulse did not alter with the gestational age. However, this velocity did increase with increasing distance from the heart (Table III). No significant correlation between the maximum increment velocity and the duration of the preceding pulse wave was found.

Table III. *Pulse wave parameters in the fetal abdominal aorta at two differnt levels of the vessel.*

	Proximal level	Distal level
Crest time, msec	121.2	109.6*
Inclination time, msec	52.1	43.2*
Maximum increment velocity, mm × sec^{-1}	17.8	21.2*

*t-statistics for paired observations, $p < 0.001$

Each value is the mean of data from 12 fetuses, each derived from 3 series of 10 pulse waves at each level. The average distance between the two levels of measurement was 25.9 mm. The mean beat intervals at proximal level and distal level were 432.5±40.1 msec and 435.3±35.0, respectively

Table IV. *Analysis of variance of pulse wave parameters.*

	Pulse wave velocity (m/sec)	Crest time/distance (msec/mm)	Maximum increment velocity/distance (mm sec^{-1} mm^{-1})
Overall±SD	1.99±0.20	0.49±0.09	0.139±0.016
Coefficient of variation			
Within fetuses, %	13.9	29.6	12.0
Between fetuses, %	10.1	18.8	11.4

Each of the 47 series (from 7 fetuses in the 35th – 37th gestational week) was calculated from 2 × 10 pulse waves at two different levels of aorta

Variation of pulse wave parameters

The intra-individual variation of the *diastolic diameter* was measured in 10 fetuses in three recordings, each comprising 10 consecutive pulse waves. The coefficient of variation within each fetus ranged from 0.8 to 8.5% and 1.0 to 10.8% of the diastolic diameter and the ΔD respectively.

The variation of the propagation velocity, the crest time and the maximum increment velocity were measured in 47 recordings from 7 fetuses at three times during the day. In order to exclude any influence due to differences in the distance from the heart, the values of the crest time and the maximum increment velocity were expressed as their relative change per mm of the aorta. The results are given in Table IV and indicate that the variation in the various parameters was greatest for crest time, probably due to the difficulty in exactly defining the peak of the curve. There were no signs of a diurnal rhythm in the parameters, and no difference was found in the variation between and within the fetuses.

DISCUSSION

The technique used in this study for quantifying the movements of vessel walls detected by ultrasound was specific and highly sensitive. The accuracy of the data obtained from the echo-tracking instrument had been tested earlier *in vitro* against an independent optical method (9) and the results obtained with the two techniques were statistically highly correlated ($r = 0.99$). The measurements were non-invasive and the transducer did not mechanically restrict the movements of the fetal aorta. The importance of leaving the target vessel undisturbed *in situ* is elucidated by comparing earlier reported data on the human carotid artery: pulsations in surgically exposed vessels amounted to 1 – 2% of the diastolic diameter (11), whereas, in intact vessels, pulsations of approximately 15% of the diastolic diameter were measured by means of ultrasound (2) or angiography (18). Moreover, in the present study the movements were recorded directly at the vessel walls, in contrast to external plethysmographic methods, where the signals are muted by passage through surrounding tissue. The continuous supervision of the target in the real-time ultrasonic image, concomitantly with the recording, guaranteed the true origin of the data received. The differential output signal derived from the simultaneous movements of the two vessel walls yielded data on the net changes in diameter, to a large extent uninfluenced by lateral dislocation of the pulsating vessel. When the intensity of the reflected echo declined below a certain threshold level, a temporary unlocking of the echo-follower occurred, before it locked to a succeeding zero-crossing of the signal. An artefact of this origin presented as a typical leap of the trace (Fig. 3), easily recognizable and excluded. The smallest amplitude of such leaps observed was 0.25 mm, which accords with the calculated distance of a half wavelength of the ultrasound used.

When the diameter of the aorta was calculated from the present data as the mean of the systolic and diastolic diameters, our values from the latter half of the third trimester agreed well with the corresponding measurement of the fetal aorta performed with subjectively placed electronic calipers in a real-time scanner (19). In the 28th – 35th week, however, recordings with the present echo-monitoring instrument gave somewhat lower values of the diameter than those measured with calipers (19). As in the latter investigation the diameter was calculated from the outer aspect of the proximal wall to the inner aspect of the distal wall, the discrepancy found suggests that the relative thickness of the image of the vessel walls early in gestation is greater than near term.

With the present equipment, calculation of the propagation velocity of the pulse wave had to use measurement of the propagation time to two different levels of the aorta at successive recordings. As the propagation time measured from the Q wave of the

fetal ECG comprised both the PEP and the true propagation time of the pulse wave along the aorta, the calculations were based upon the assumption of a constant duration of PEP and were therefore restricted to periods of fetal rest with regular fetal heart rate. Any variation in the PEP was further minimized by normalizing the periods against the length of the beat-to-beat interval, according to the formula given by Organ et al. (22). However, the variation in the PEP remains a factor of instability. The present data on the propagation velocity must therefore be regarded as preliminary, awaiting improved equipment allowing simultaneous recording of diameter pulses at two different levels of the vessel.

The relative amplitude of the diameter pulsations for the entire group of fetuses was, on average, 19% of the diastolic diameter. This accords well with recent observations performed with M-mode ultrasound on a human fetus at term (5) and exceeds data obtained with a time-distance recorder (7). The low time resolution of the latter instrument, due to the limited frame rate (40 Hz) of the scanner connected to it, is probably responsible for the observed discrepancy in the results. The absolute magnitude of the pulses of the aorta was unchanged over the gestational period studied. Expressed as percentage expansion from the diastolic diameter, increasing with age, the relative amplitude of the pulses diminished. This decline might reflect a change in the structure of the vessel wall, though an increase in the content of elastin during late gestation observed in the aortic wall (3) is somewhat contradictory to the present observation. An increase in the diastolic intraluminal pressure straining the vessel wall and thereby diminishing its compliance is another potential factor possibly causing a reduction in the pulsations. Although the aortic intraluminal pressure of the human fetus *in utero* is not known, in several mammalian species the mean arterial blood pressure has been reported to rise with gestational age before birth (6).

The pulsating increment of the transverse area of the aorta increased by 29% from the group with a median age of 33 weeks to the group of a median age of 37 weeks, which is interesting and accords well with the estimated increment (40%) of the mean fetal weight *in utero* during this period (8). Wladimiroff and co-workers calculated by ultrasonic assessment of the cardiac geometry a 60% rise in the left ventricular output over approximately the same fetal age interval (26). However, this figure also included the part of the ventricular output flowing via the carotid and the subclavian vessels but not the contribution from the ductus arteriosus to the aortic flow, both flows presumably affecting the pulsations in the descending aorta. In relation to the estimated fetal weight, the magnitude of the area pulsations remained constant during the gestational period studied here. This observation agrees with the recent report of a constant fetal aortic flow per kg body weight calculated from pulsed Doppler sonic measurements (19).

The viscoelastic properties of vessel walls are reflected in the pattern of pulse curves. Thus, in the presence of arteriosclerotic disease, the crest time and the inclination time of plethysmographic curves obtained from peripheral vessels are prolonged (27). The values of these two parameters in the fetal aorta expressed as a percentage of the overall cycle duration are less than the corresponding values from peripheral vessels in adults (27). Considering that crest time and inclination time both decrease when the pulse wave travels along the descending aorta, the differences between fetal and adult values are further augmented and suggest a greater degree of compliance in the fetal than in the adult aortic wall. Although data are not available on any regional differences in the composition of the human fetal aorta, it is of interest to note that in adult dog the relative content of elastin in the wall of the descending aorta has been found to diminish rapidly in the distal direction (13).

The duration of the previous beat interval exerted a profound influence on several characteristics of the pulse wave. The diastolic diameter diminished in inverse proportion to duration of the previous beat interval, allowing the vessel more time to relax. On the other hand, the systolic diameter was found not to vary with the length of the preceding beat interval. A similar phenomenon has been observed in the anteroposterior diameter of the left ventricle in the end-systole and in diastole during heart rate variation in fetal lamb (15).

The positive non-linear relationship between the preceding beat interval and the amplitude of the aortic diameter swings (Fig. 4) affects our concept of fetal cardiovascular dynamics. As the amplitude of the diameter pulsation reflects the intravascular pulse pressure (24) and thus the magnitude of the ventricular stroke volume (12), the data suggest that an increased end-diastolic ventricular volume due to better filling augments the stroke volume, thereby implying that the Frank-Starling mechanism is effective also during fetal life. The enhanced pulse amplitude ob-

served in connection with a reduced heart rate might, of course, also be ascribed to a force-interval relationship of the myocardium present in the fetal heart (1). Our observation is not consistent with the hitherto prevailing concept that the fetal heart has little ability to increase its stroke volume and that the cardiac output is mainly dependent on the high heart rate (23), but it is supported by other studies on fetal lambs (16). The present work corroborates recent results obtained by Doppler ultrasound measurement in the aorta of the human fetus, demonstrating that prolonged beat intervals augment the flow velocity (19).

The new data presented in this report describe the pulsatile behavior of the fetal descending aorta during clinically normal conditions. The complex nature of the diameter pulse is realized and analyses were therefore performed using already accepted methods from clinical physiology. However, the results so far accord with corresponding data from adult man and other species (20) and suggest that changes in the intra-aortic pressure occur *in utero* due to altered cardiac function and/or altered peripheral resistance. These data will serve as a basis for subsequent studies on pathological pregnancies and on the effect of maternal smoking on fetal circulation.

ACKNOWLEDGEMENTS

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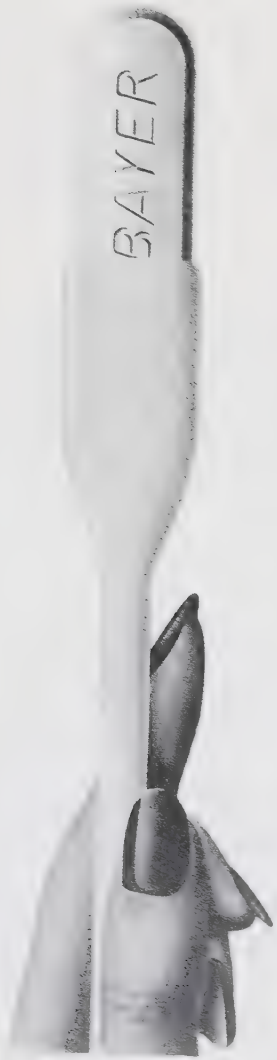

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Acute Effects of Maternal Smoking on Fetal Breathing and Movements

POUL SINDBERG ERIKSEN, MD, GERHARD GENNSER, MD, PhD, OLOF LÖFGREN, MD, PhD, AND KARIN NILSSON, MSc

The acute effects of cigarette smoking on fetal breathing movements and fetal movements were determined with a real-time ultrasound system in 10 healthy habitually smoking women in late gestation. The study was carried out for 1 hour before and 1 hour after the woman smoked a single cigarette. The maternal blood glucose concentration was maintained at a raised postprandial level through the study. After smoking, a significant increase in the rate of fetal breathing movements ($P < .05$) appeared together with a reduction in the short time variability of the breath-to-breath intervals ($P < .05$). The number of epochs without fetal breathing movements or fetal trunk and limb movements increased after smoking ($P < .05$), indicating a change in the spacing of these fetal activities. The increased breathing rate and number of apneic epochs were both correlated to maternal nicotine levels. These observations suggest an acute influence on the fetal behavioral state of maternal smoking. ***(Obstet Gynecol 61:367, 1983)***

Habitual smoking among pregnant women is frequent despite antitobacco campaigns,[1,2] thus presenting a quantitatively important environmental problem during gestation. The chronic effects of maternal smoking on the fetus are well documented,[2–4] but less attention has been paid to the acute effects of smoking on the fetal vital signs. Methods are now available to study noninvasively various aspects of fetal physiology. Ultrasound scan has been used to monitor fetal breathing movements as well as trunk and limb movements.

Recording of fetal breathing movements has been suggested for surveillance of high-risk pregnancies,[5,6] and the subjective daily count of fetal movements has been recommended for screening of the pregnant population.[7] In view of the potential clinical use of these fetal activities, the present study evaluates the acute effects on the fetal breathing movements and fetal movements of the pregnant woman smoking a single cigarette in the last trimester of gestation.

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Materials and Methods

Informed consent was obtained from 10 women in the 34th to 40th week of uncomplicated gestation. In all fetuses a normal growth profile was ascertained by ultrasound fetometry in the 17th and the 33rd weeks. At the investigation, the fetuses were normal according to routine clinical criteria; none developed distress during the subsequent parturition.

All the women were habitual smokers with a daily consumption of 1 to 30 cigarettes; they were urged not to smoke for 12 hours before the study. The investigations started at 1230 hours after the women had had a carbohydrate-rich lunch. To keep the maternal blood sugar at the postprandial level throughout the 2-hour study, the women were encouraged to have a glucose-sweetened soft drink and/or eat a chocolate bar intermittently.

The women were recumbent in left lateral position during the study. Fetal breathing movements were detected by real-time ultrasonography, a longitudinal section of the fetus being continuously observed during the study on a video monitor, allowing the operator to identify the fetal breathing movements and event-marking them. For simultaneous objective quantification of the fetal breathing movements, a time-distance recorder coupled to the ultrasound scanner was used, as has been previously described.[8] A manual event marker was used for indicating the occurrence of sonically observed gross fetal movements other than breathing movements. The signals of the gross movements and the fetal breathing movements were fed into a multichannel pen recorder and stored by a 4-channel magnetic tape recorder.

Maternal transcutaneous Po_2 ($P_{tc}O_2$) was measured

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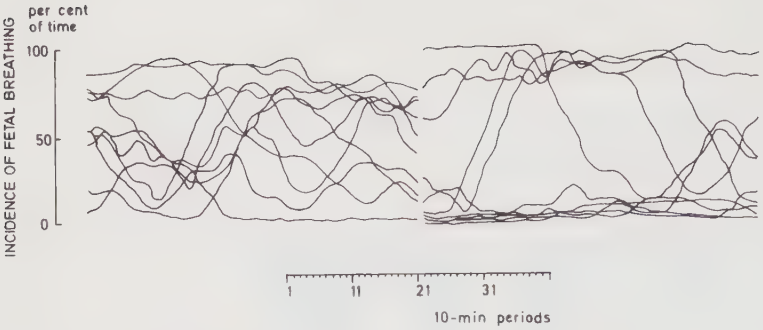

Figure 1. Smoothed curves of the incidence of fetal breathing movements in 10 women before (left traces) and after (right traces) smoking, compiled as the moving average of 10-minute periods with 1-minute sampling rate. The real time of the pause during smoking 1 cigarette averaged 5 minutes.

throughout the study via an electrode attached to the skin of the left armpit and feeding a central instrument.* A continuous record was obtained both of $P_{tc}O_2$ and of the energy level needed to keep the electrode at a constant temperature (44.5C). Free-flowing blood was collected from an indwelling cannula in one antecubital vein at t = −60 minutes, −30 minutes, 0 minutes, +10 minutes, +30 minutes, and +60 minutes (timed from the start of smoking) and glucose was measured in the samples. The carboxyhemoglobin percentage and the nicotine concentration were determined in blood samples taken at t = 0 minutes, +10 minutes, and +30 minutes.

Nicotine was measured by a method comprising gas-liquid chromatography and mass spectrometry;[9] The intraassay coefficient of variation was 8.0% and a control group of nonsmokers had a mean value of 5 μg/liter blood. After a 60-minute control period, the women smoked a cigarette yielding 1.6 mg nicotine and 17 mg carbon monoxide in the smoke as stated by the manufacturer. Following the smoking, the study proceeded for another hour.

To evaluate the parameters, the presmoking control period and the period after smoking were each divided into 12 5-minute epochs. The incidence of the fetal breathing movements and the gross movements was calculated from the echographic tracings and the event-marked chart record as the percentage of each 5-minute epoch spent in the particular movement. When both gross movements and breathing movements were detected simultaneously in the fetus, the activity was classified as fetal breathing movements only. The average incidence of concomitant breathing and gross movements in the fetus in the 3rd trimester of gestation has been found previously to be 2% of the time observed.[10]

The breath-to-breath intervals were measured manually on the paper records by means of a digitizer connected to a microcomputer. Breath-to-breath intervals were measured for periods of continuous breathing; no fetal apneic periods (arbitrarily defined as nonbreathing > 6 seconds) were included in the calculations. The coefficient of variation of the intervals (SD/mean × 100) and the SD of the breath-to-breath interval differences (SD of $T_2 - T_1$, $T_3 - T_2$, etc.) were also calculated.

The results are given as the means and the SD of the stated time period. Statistical analysis used the Pearson correlation, the Wilcoxon matched-pairs signed-ranks test, and the Student *t*-test.

Results

The attempt to keep the maternal blood glucose at a high level throughout the observation period was successful. In one case, no glucose values were obtained because of a technical fault; all the other women during the first half hour after smoking had levels exceeding 4.5 mmol/liter. There was no statistical difference between the overall means of blood glucose levels before and after smoking. The concentration of carboxyhemoglobin before smoking was related to the average cigarette consumption stated by the particular woman ($r = .69$; $P < .01$); the mean level rose markedly during the first 10 minutes after smoking and remained at the high level 20 minutes later.

The basal nicotine concentration in the maternal blood before smoking ranged from 0 to 5 μg/liter, being unrelated to the daily cigarette consumption of the woman. Ten minutes after the start of smoking, the nicotine concentration had markedly increased to 19.35 ± 2.38 μg/liter; 20 minutes later, the average concentration had dropped to half this level. The elimination rate of nicotine from the blood circulation between 10 minutes and 30 minutes after the start of smoking was highly correlated to the attained maximum level (r =

* TCM 1 Transcutan Po_2 meter, Radiometer, Copenhagen, Denmark.

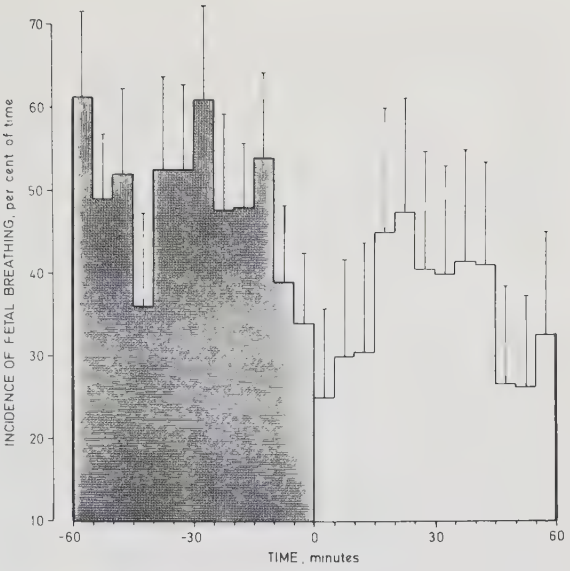

Figure 2. The mean incidence of fetal breathing movements per 5-minute period before and after smoking in 10 women. Vertical bars denote SEM.

.90; $P < .001$). In each woman, the $P_{tc}O_2$ remained approximately constant throughout the study. The tension calculated from the 5 consecutive minute-to-minute values immediately preceding smoking was 8.5 ± 3.0 kPa/liter; immediately after the end of smoking the corresponding value was 9.0 ± 3.1 kPa/liter. Only 2 women had a reduction of the transcutaneous oxygen tension exceeding 1.4 kPa/liter.

Table 1. Parameters of Fetal Breathing Movements and Fetal Movements

Time	Before smoking −60–0 min	After smoking 0–60 min
Fetal breathing movements		
Incidence (% of time)	48.9 ± 8.9	35.5 ± 7.8
SD of interval differences (sec)	0.25 ± 0.04	0.21 ± 0.05*
Coefficient of variation (%)	24.9 ± 3.3	25.3 ± 4.0
No. of epochs with apnea	15/120	48/120*
Fetal movements		
Incidence (% of time)	12.5 ± 3.5	13.5 ± 7.8
No. of epochs without fetal movements	14/120	39/120*

* $P < .05$ (Wilcoxon matched-pairs signed-ranks test).
Values are mean ± SD.

Fetal Breathing Movements

The start of the 2-hour periods of the investigation was found to be randomly time-positioned in relation to the spontaneous periods of breathing activity in the fetus (Figure 1). This is also illustrated by the observation that the mean incidence of fetal breathing movements among the patients before smoking in any 5-minute epoch was not significantly different from that of all the other periods (Figure 2).

An overall high incidence of fetal breathing movements (group mean, 48.9%) was noted during the control period (Table 1); both before and after smoking there was a large variation between patients and also between the various epochs (Figure 2). When comparing the 60-minute period before and after smoking, there was no significant difference in the overall fetal breathing movements incidence (paired t test: $P > .05$).

The number of epochs during which fetal breathing movements were not detected increased after smoking. During the control period, there was no breathing observed in 12.5% (15 of 120) of the epochs. After smoking, the corresponding figure was 40.0% (48 of 120 epochs). The increase of apneic epochs was significant in a paired comparison between the periods (Table 1), and was positively correlated to the increase from the control value in maternal nicotine concentration at 30 minutes after smoking ($r = .75$; $P = .012$).

Table 2. Mean Fetal Breath-to-Breath Intervals Before and After Smoking in 7 Patients

Before smoking −60–0 min	After smoking 0–60 min
1.17 sec (3.141)	0.99* sec (2.985)

* $P < .05$ (Wilcoxon matched-pairs signed-ranks test).
Figures in parentheses denote the number of intervals counted.

In 60 of the 120 5-minute epochs during the control time and in 43 of the 120 epochs of the postsmoking period, fetal breathing movements were recorded with sufficient quality to define the end of inspiration in the individual breathing cycles on the charts. These epochs contained periods of continuous breathing during which the breaths followed each other with intervals of less than 6 seconds, allowing the calculation of breath-to-breath intervals. In 7 women with periods of continuous fetal breathing both before and after smoking the mean breath-to-breath intervals decreased significantly after smoking by 15% from 1.17 seconds (Table 2).

The breath-to-breath intervals and their change after smoking were not correlated to the initial levels of carboxyhemoglobin, nicotine, glucose, or $P_{tc}O_2$, to the number of cigarettes consumed per day, or to the changes in carboxyhemoglobin after smoking. A negative correlation was found between the breath-to-breath interval and the decline of the nicotine concentration between 10 and 30 minutes after smoking ($r = -.818$; $P < .05$).

The variability of the breath-to-breath intervals in all 103 epochs indicated, calculated as the mean coefficient of variation, did not change with smoking in the group of 7 patients. The standard deviation of the breath-to-breath interval differences between the control period and the period after smoking fell significantly ($P < .05$) (Table 1).

Fetal Trunk and Limb Movements

The occurrence of fetal gross movements was apparently not influenced by the maternal smoking (Table 1). The number of epochs with total absence of gross fetal movements before smoking (14/120, 11.7%) increased significantly ($P < .05$) during the postsmoking hour to 39/120 (32.5%). The difference in the number of epochs with total inactivity between the presmoking and the postsmoking periods persisted (2/60 versus 12/60; $P < .01$) also when the epochs were increased to 10 minutes' duration. This indicated that the fetal gross movements became aggregated into marked periodicity after smoking. This change of pattern was also suggested by the apparent increase in the mean duration of periods of movements from 14.9 ± 1.6 seconds before smoking to 23.3 ± 4.3 seconds after smoking; however, this was not a significant difference. Neither did the longest duration of a movement period (51.9 ± 7.5 seconds before smoking and 100.0 ± 26.2 seconds after smoking) change significantly.

Discussion

The real-time B-mode ultrasonic system combined with a time-distance recorder[8] in the present study ascertains reliable data on fetal breathing movements and also provides a basis for evaluation of the time course of these movements. The incidence of fetal breathing movements has been shown to display several natural rhythms.[11] Of these, the variability with rest-activity periods of an average cycle length of 1 to 1.5 hours strongly influences the level of fetal breathing movement incidence found in short-term recordings.[12,13] For adequate results, the recording time must therefore exceed the length of at least 1 complete cycle: it was recently demonstrated that the minimum time for obtaining an estimate of the fetal breathing movements during the second and third hours after a major meal is 45 minutes.[12] The demand for a sufficiently long period of recording was met in the present study (60-minute control time + 60-minute postsmoking time). Moreover, care was taken to keep an elevated maternal blood glucose level all through the study, this having been repeatedly demonstrated as a single potent factor augmenting fetal breathing.[14,15] These precautions aimed to exclude 2 major causes of spontaneous variation in the fetal breathing movements incidence.

The incidence of fetal breathing movements during the control period was higher than the average incidence given for fetuses in normal gestation during long-term registration.[11] However, the postprandial state of the present study is comparable to that after an oral glucose load. In fact, the observed fetal breathing movement incidence during the control period is very close to that reported for fetuses during induced hyperglycemia.[14,15] Also, the occurrence of 5-minute epochs with no detected fetal breathing movements was 12.5% of the 120 epochs during the control period. Natale et al[15] registered 15-minute epochs and found 3% of them without fetal breathing movements during 1 to 3 hours after an oral glucose load, against 22 to 25% in the fasting state. As the time basis is different, their figures are not directly comparable with the present results, but the qualitative changes suggest that maternal fasting affects the occurrence of fetal breathing movements in a manner similar to smoking.

No effect on the fetal breathing movement incidence exerted by smoking could be detected in the group of women when the entire observation periods for control time and test time were compared. A similar conclusion was recently reached by an Oxford group,[16] which measured fetal breathing movements indirectly by their effect on the flow velocity in the great veins below the fetal heart. These new results are at variance with earlier reports,[17,18] the discrepancy being attributable to the insufficiency of formerly used monitoring techniques. However, several indications were now found on an altered fetal breathing pattern after smoking. Thus, the increase of the proportion of epochs with total apnea after smoking suggests that the fetal breathing was concentrated into fewer epochs with a mean higher incidence of breathing, ie, an increased periodicity. A trend to increased stability of the breathing rhythm was noted, illustrated by a significant decrease after smoking in the SD of the interval differences. The significant reduction of the average breath-to-breath interval was another evident effect of the smoking that was corroborated by a recent similar observation.[16] The validity of the obtained records of the fetal breathing movements incidence was further evaluated by investigating the distribution of the rest-activity periods of the 10 fetuses along the time axis. The random onset of the study in relation to the phase of the individual rest-activity cycle ascertained that the patients were a representative sample.

The mechanisms by which maternal smoking might affect the homeostasis of the human fetus have been repeatedly studied.[19] Considering the activation of the adrenergic system caused by nicotine, a constrictor activity of this agent has been assumed on the uterine vessels with resulting impairment of the placental perfusion. A direct action on the fetus by nicotine transferred across the placenta is suggested by the increased breathing rate, which is also observed in the smoking adult. There was a trend of the mean $P_{tc}O_2$ to increase after smoking. This was apparently related to the increase of the maternal breathing rate and not caused by changes in the skin circulation, as the hyperemia caused by the heated electrode should produce an optimal arterialization of the capillary blood. Furthermore, there was no change in the mean energy supply to keep the electrode temperature constant. The change in the $P_{tc}O_2$ level was discrete and not as obvious as those changes reported in mothers intermittently hyperventilating during labor.[20]

The incompletely known transfer and metabolism of nicotine during pregnancy contributes to the difficulties in evaluating the effects of smoking on the human fetus. In the present group of women, a large range of attained maximum blood nicotine levels was found; this is presumably due to differences in inhaling technique, as this has been shown to be a major determinant of the absorption of nicotine during smoking.[21] The measurements demonstrate that during late pregnancy the rate of decline of the circulation maternal nicotine concentration from its peak value was directly related to the maximum level of blood nicotine, as has also been demonstrated in men in arterial blood.[22] Smoking induces the enzymes responsible for the degradation of nicotine[23] and therefore might occasion a more rapid elimination of nicotine in women with higher nicotine intake.

The fetal trunk and limb movements were monitored visually from the ultrasound screen by a trained observer. The longitudinal section of the fetus covered by the linear array transducer includes only a portion of the fetal trunk and limbs, but movements of fetal parts outside the image can often be recognized by the passive dislocation of visible parts of the fetus. Earlier, a depressant effect of smoking on the number of fetal movements had been reported.[16,24] These studies were carried out with subjective recording of the fetal movements by the mother; however, a good agreement was found between the kick counts and the number of movements recorded with the aid of real-time ultrasound, provided that the fetal activity exceeded a certain level.[25] In the present investigation the incidence of fetal movements was measured; this has been claimed to be more reliable than counting the number of movements, particularly when these are of long duration.[25] The finding after smoking of an unchanged incidence of movements together with an increase in the number of epochs without fetal activity suggests an altered pattern of fetal movements with a higher degree of clustering. In view of this consideration, the reported reduction of the number of movements after smoking[16,24] does not really conflict with the present data, as it can rightly be presumed that the maternal ability to discriminate fetal movements from each other is impaired when these movements are grouped into coherent periods. The altered time course of fetal movements after maternal smoking might represent a change in the behavioral state of the fetus, but the present data do not permit an evaluation of such a hypothesis.

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ACUTE EFFECTS OF MATERNAL SMOKING ON FETAL HEART BEAT INTERVALS

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Abstract. The purpose of this study was to analyse the acute effects of maternal cigarette smoking on the fetal heart beat intervals and their variability during the last trimester of a normal gestation. The fetal heart beat intervals were monitored continuously by abdominal electrocardiography for 60 min before and 60 min after smoking in 10 pregnant women. The mean intervals, their long-term variability (SD) and short-term variability (standard deviation of interval differences (SDID)), calculated for 30-sec periods, showed a steady state before smoking. During the control period, the mean beat interval was negatively correlated with daily cigarette consumption and the short-term variability was positively correlated with the maternal plasma nicotine level. After smoking, the mean beat interval and the short-term variability decreased transiently, the values of both these parameters being positively correlated with the maternal nicotine values before smoking. The acute response of fetal heart beat intervals and their variability to one cigarette is distinct but transient, and the results suggest that the effects are modified by the chronic smoking habits of the women.

Key words: Maternal smoking, acute effects, fetal heart rate response

The use of fetal heart rate (FHR) monitoring for antenatal surveillance has become widespread, both in normal and high-risk pregnancies (14), and the variability of the fetal heart rate has been considered as a parameter for an indicating fetal distress (16). Several factors are known to influence the heart beat interval in the fetus (9), maternal smoking being one such intervention (2, 12), which potentially interferes with the clinical interpretation of fetal cardiograms. The documented high incidence of smoking also among pregnant women (10) emphasizes the magnitude of this problem. It was the purpose of the present study to thoroughly evaluate the acute influence of maternal smoking of a single cigarette on the duration of the beat-to-beat intervals and their long- and short-term variability in the human fetus.

MATERIALS AND METHODS

The study was performed on 10 normal pregnant women who gave their informed consent. All pregnancies were singletons near term (34–40 weeks) with an uneventful obstetric history as well as a normal outcome of the gestation. Characteristic data of the pregnant women and the subsequently born babies are given in Tables I and II. The women were chronic smokers, with maintained smoking habits during the pregnancy (median 14, range 1–23 cigarettes per day); after abstinence of at least 12 hours, the women smoked one standard cigarette (average yield 1.6 mg nicotine and 17 mg carbon monoxide). The maternal COHb concentration in blood rose considerably from the basal level (range 0.20–1.01%) to 0.94–2.04% after smoking. FHR was recorded continuously with the women in a semirecumbent position for 60 min before smoking and 60 min after smoking; during smoking (average duration 5 min) the recording was interrupted for technical reasons but the woman did not change her resting position. Fetal electrocardiographic (FECG) signals were registered via abdominal silver/silvercloride electrodes positioned after careful preparation of the skin and were detected by a cardiotachograph (Kranzbühler FM 5000) which separated the fetal from the maternal complexes by a blanking procedure. Square-wave pulses triggered by the fetal signals were stored on magnetic tape; the inter-beat intervals were also transformed into an analog signal representing the instantaneous FHR on a fetal cardiotocogram.

Table I. *Maternal characteristics.*

	Mean±SD
Maternal age, years	27.7±6.3
Parity	1.7±0.8
Gestational age at time of study, weeks	37.0±2.1

n = 10

Table II. *Fetal outcome data.*

Birth weight, g (mean±SD)	3 310±557
Gestational age at birth, weeks (mean±SD)	39.3±1.3
Apgar score, range	
1 minute	8–10
5 minute	9–10

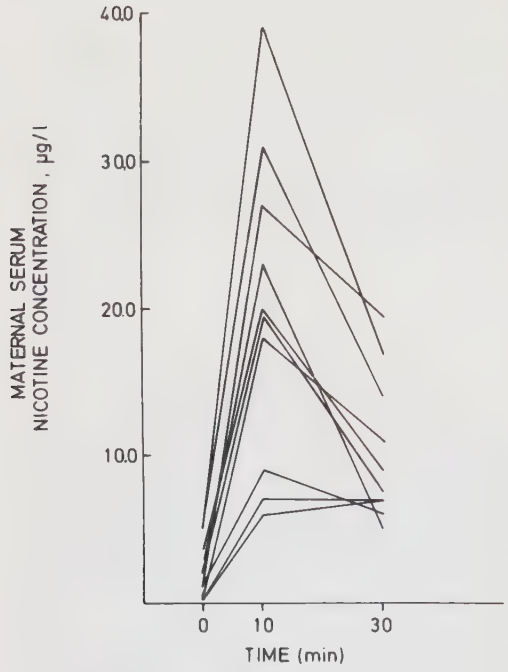

Fig. 1. Nicotine concentration in maternal serum in relation to time after smoking one cigarette (n = 10).

Fetal breathing movements and gross body movements of the trunk and limbs were monitored continuously on a real-time ultrasound scanner and recorded by event-marking on two channels of a pen-recorder. For validation the fetal breathing movements were simultaneously recorded objectively via a time-distance recorder (Teltec) yielding a continuous analog signal representing the movements of a selected fetal trunk wall (8). The incidence of each type of movement was calculated as the percentage of each 5-min epoch of the observation time which the fetus spent executing the particular movement.

Nicotine was analysed in maternal venous blood, sampled just before smoking and 10 min and 30 min after the onset of smoking, with a method comprising gas-liquid chromatography and mass-spectrometry (assay coefficient of variation 8.0%). The control nicotine concentration in maternal plasma was 1.75±0.53 µg/l; 10 min after the onset of smoking, 19.35±2.38 µg/l and 20 min later, 10.35±1.55 µg/l (Fig. 1).

The instantaneous fetal heart rate used in clinical obstetrics and expressed as beats per min is the inverted value of the beat-to-beat (or R-R) interval detected by the cardiotocograph. Recent international reports on fetal heart rate variability give the measured values based on the beat-to-beat intervals (see 18) and the present study complies with this convention. Those who want the invervals transformed into instantaneous fetal heart rate are referred to Table III.

The beat-to-beat intervals of the fetal heart were evaluated by feeding the tape-recordings of the recognized fetal signals into a computer (PDP8/E, Digital Equipment Corporation) at four times the real-time speed. The R-R intervals were measured to a resolution of 100 µsec in real time; they were subjected to an artefact rejection procedure before being finally accepted by the computer.

To evaluate the time course of changes in the beat intervals, the control period and the post-smoking period were each divided into twelve 5-min epochs. The parameters for these epochs are presented as the mean values from the ten 30-sec periods contained in each particular epoch. The index of long-term variability used was the standard deviation of the individual fetal heart beat intervals (3, 21), while the short-term variability was expressed as the standard deviation of the consecutive R-R interval differences (SD of $T_1 - T_2$, $T_2 - T_3$ ...) (SDID) (21).

Statistical analyses were carried out using the Student's t-test, the Wilcoxon matched-pairs signed-ranks test, and the Pearson correlation.

Table III. *Mean beat-to-beat intervals (mean), their long-term (SD) and short-term (SDID) variability (msec), and instantaneous heart rate (beats per min) per 5-min epoch in 10 fetuses.*

	5-min epoch no.											
	1	2	3	4	5	6	7	8	9	10	11	12
Before smoking												
Mean	425	420	422	415	419	414	417	412	414	419	417	409
SD	24.7	26.5	24.4	27.1	27.2	32.2	26.0	27.4	24.0	29.2	27.1	23.6
SDID	16.6	16.0	15.5	16.0	15.6	15.4	15.7	15.6	15.3	15.7	15.8	15.2
Beats/min	141	142	142	145	143	145	144	146	145	143	144	147
After smoking												
Mean	372**	385*	393*	397	400	404	405	412	412	417	422	415
SD	27.4	25.9	23.5	25.2	27.9	24.8	28.2	23.1	26.8	23.6	26.8	22.4
SDID	13.0**	13.5*	13.9	13.7*	14.2	14.4	14.8	14.7	15.1	15.6	15.9	16.1
Beats/min	161**	156*	153*	151	150	149	148	146	146	144	142	145

Significance of difference (Wilcoxon matched-pairs signed-ranks test) is given for comparison between each post-smoking epoch 1 – 12, and the presmoking control epoch of corresponding number of order. *$p < 0.05$; **$p < 0.01$.

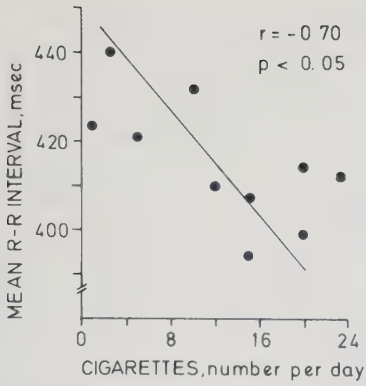

Fig. 2 A. Relation between mean fetal R-R interval during the control period and average maternal cigarette consumption in 10 women.

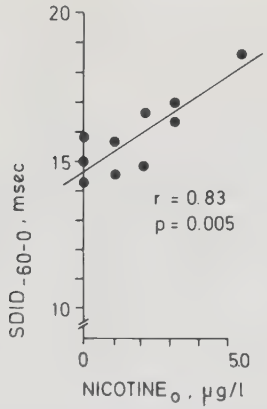

Fig. 2 B. Relation between mean short-term variability (SDID) in the control period and concomitant concentration of nicotine in maternal blood (n = 10).

RESULTS

Before smoking

The statistical analyses of the fetal heart beat intervals were based upon 128000 accepted beat-to-beat intervals, which represent 73% of the total number of intervals recorded during the 2-hour study in the ten women. During the investigation, there was, apart from the transient changes appearing after smoking, no progressive alteration in the fetal heart beat intervals or their variability. The steady-state is shown in Table III. Moreover, this is illustrated by the finding that the overall mean beat interval of each 5-min epoch during the period 30 min − 60 min after smoking, when the visible effect of smoking on the heart beat intervals had subsided, was not significantly different from that of the corresponding period before smoking. This agreement pertains also to the different expressions of the interval variability. A slight downward trend in the length of the beat interval was noticeable during the last 5-min epoch before smoking but was not statistically significant. A negative correlation was noted between the mean beat interval in the control period and the daily cigarette consumption of the woman ($r = -0.70$; $p < 0.05$) (Fig. 2A), i.e. the heavy smokers had a higher mean FHR than the light smokers. Furthermore, the short-term variability during the control period was positively correlated with the nicotine level in maternal blood before smoking ($r = 0.84$; $p = 0.005$) (Fig. 2B). Five women had, before smoking, a large variability in the incidence of fetal breathing movements, which ranged from zero to over 60% of the time in the different periods. When comparing the fetal heart beat intervals in 5-min epochs of total apnea with those in epochs of high (>60% of time) incidence of fetal breathing, a significantly lower short-term variability was found ($p < 0.02$; rank sum test for two samples) in the former group (Table IV); no difference in the long-term variability of the intervals was observed between the groups.

After smoking

Even during the first 5-min epoch after smoking, the mean duration of the fetal heart beat intervals decreased (Fig. 3). The first three epochs after smoking were compared with the first three control epochs in order to avoid any reaction of expectation prior to smoking. In this comparison, the beat interval averaged for all 10 women was significantly shorter after

Table IV. *Short-term variability (SDID) in relation to fetal breathing movements (FBM), msec.*

Pat. no.	Epoch without FBM	Epoch with ≥60% FBM
1	15.7 (2)	17.7 (1)
2	15.6 (2)	17.9 (6)
5	15.8 (2)	16.5 (3)
7	13.3 (1)	16.6 (3)
9	16.2 (1)	16.8 (3)
Mean±SD	15.3±1.2	17.1±0.7*

*$p < 0.02$. Each value is the mean of approximately 500 beat intervals per epoch; the number of epochs is given in parentheses

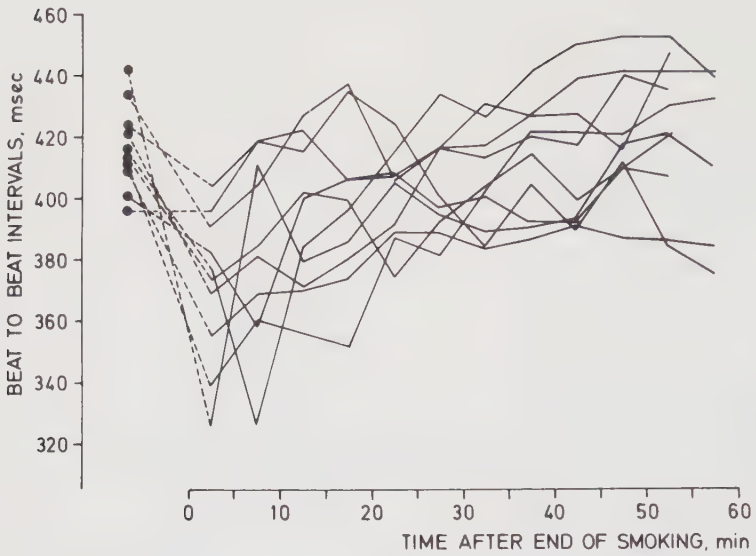

Fig. 3. Mean heart beat intervals calculated for 5-min periods after one cigarette in 10 fetuses. •, mean beat interval in preceding 60-min control period for each patient.

smoking (Table III). The mean beat intervals during the 30 min directly after smoking were positively correlated with the nicotine concentration in maternal blood before smoking ($r = 0.75$; $p = 0.013$), but not with the nicotine concentration at 10 min or 30 min after smoking.

The short-term variability decreased after smoking, being significantly lowered during three of the first four 5-min epochs, when compared with the corresponding control epochs. A positive correlation was found between the short-term variability during the first 30 min after smoking and the maternal blood-nicotine concentration in the pre-smoking period ($r = 0.80$; $p < 0.01$). The long-term variability was not affected by the smoking. On visual analysis of the fetal cardiotocograms, brief accelerations in the heart rate were observed in 9 of the 10 cases, both during and after the period of smoking.

DISCUSSION

The intervals between the fetal heart beats vary considerably in length, even during apparently physiological conditions. The study of the variation in the fetal heart beat intervals has been beset by two major obstacles: the difficulty of non-invasive detection of the heart beats, and the lack of generally accepted numerical expressions of the variability. For collecting of the necessary data from the fetus, abdominal FECG has the advantage over Doppler ultrasound and phonocardiography for obtaining precise measurements of the heart cycle length (20), and has been used in several studies to quantify the fetal heart rate and its variability (4, 21).

Several methods have been devised for quantitative definition of the variability of the fetal heart beat intervals. The discrimination between the long-term and short-term variability has been widely adopted (5, 21) and has the advantage of being related to clinical experience. Recently, analytical programs have been presented, making possible computerized recognition of the variability (19). The standard deviation of the heart beat intervals is a recognized index of the long-term variability (3, 21) and it has been shown to increase with the duration of observation, both in fetal lambs (3) and in the human fetus (21). In the present study, the long-term and the short-term variability of the intervals during the control period were on average twice the value of that obtained in the study of Wheeler et al. (21) when considering the same sampling period (30 sec). A reasonable cause of this difference is the different limits set to demarcate the intervals used in the analysis, as these were set considerably wider in the present investigation in order to retain possible changes induced by smoking.

The short-term variability comprises only one-tenth of the overall variability of the intervals (19) and is influenced by factors such as the gestational

age (19) and fetal breathing movements (4). In the present data, no correlation was found between the mean heart beat intervals and the incidence of fetal breathing movements but, in agreement with an earlier report (22), an increase in the short-term variability occured with fetal breathing in the control period. Interestingly, the increase in the short-term variability of the fetal R-R intervals has been observed prior to the onset of the detected fetal breathing movements (4).

Maternal smoking caused a transient reduction in the short-term variability of the beat intervals. It is not evident that this decreased variability can be taken as a sign of fetal compromise, although several studies have indicated a relationship between 'silent pattern' in antenatal cardiotocographic recordings and an unfavorable outcome of the pregnancy (16). Recent work suggests that decreased variation accompanies chronic hypoxia in fetal monkeys (9), fetal lambs (3) and human fetuses (6), while increased variation has been observed in acute hypoxia in fetal lambs (3, 17). It should be emphasized that in the present study the post-smoking reduction in the variability of the fetal heart beat intervals was related to the baseline variation only. Accelerations in the fetal heart rate (associated with gross fetal trunk and limb movements) were observed also during these periods of low variation; these cardiotocographic traces were thus not interpreted as indicating fetal compromise. The short duration of the reduced variability observed after smoking makes it less likely that this acute effect will interfere with the interpretation of antenatal cardiotocography in clinical practice, provided that the interval after smoking exceeds 50 min, this period being the maximum duration of smoking effect observed in the study. A similar duration of the effect of maternal smoking on the fetal heart rate has been observed earlier (2). The continued presence of FHR accelerations in our study also accords with previous work demonstrating that, in chronically smoking pregnant women, one cigarette did not acutely increase the incidence of non-reactive non-stress test (1), although these women did exhibit a generally increased incidence of such tests in the absence of fetal distress (11).

The transient decrease in mean fetal heart beat intervals and their variability illustrates an acute effect of one cigarette in the habitually smoking pregnant woman. On the other hand, the finding in the control period of a higher mean fetal heart rate in heavy smokers than in light smokers (Fig. 2A) suggests a chronic effect of smoking on the regulation of the fetal heart beat intervals. This concept is emphasized by the relationship of the post-smoking values of the mean beat interval and the short-term variability to the maternal plasma nicotine concentration before smoking. Neither the mean beat interval before smoking nor the acute response of the intervals to smoking was dependent on the simultaneous maternal concentration of circulating nicotine, suggesting that factors other than nicotine contained in maternal blood might be responsible for the effect on the fetal heart rate.

A positive correlation between the concentration of carboxyhemoglobin in the control period in these women and their average daily cigarette consumption has been found (15), and the ability of carbon monoxide to diffuse rather slowly across the placenta to give a fetal carboxyhemoglobin concentration reflecting that of the mother (7) hints at a possible role of this compound in altering the fetal heart beat intervals. The idea of positive chronotropic substances other than nicotine in cigarette smoke has recently been supported by studies in adults showing a raised heart rate even after smoking tobacco cigarettes with an ultra-low nicotine content (13).

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ACUTE RESPONSES TO MATERNAL SMOKING OF THE PULSATILE MOVEMENTS IN FETAL AORTA

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Abstract. In order to further characterize the acute cardiovascular responses of the human fetus to maternal smoking, 17 women in late pregnancy were studied after smoking a single cigarette. The pulsations of the fetal descending aorta were recorded by means of an ultrasound scanner connected to a phase-locked echo-tracking instrument; the fetal ECG was recorded from abdominal electrodes. Both the level and the wave-form of the diameter pulse curve changed typically 3-25 min after the onset of smoking, concomitant with an increase in maternal and fetal heart rate. Apparent diastolic diameter and pulse amplitude increased, while the ascending part of the curve increased in slope and decreased in duration; the late decremental velocity was reduced. The propagation time from the onset of the fetal Q-wave to the arrival of the pulse wave at the site of recording was reduced. This study demonstrates for the first time the acute effects of maternal smoking on the pulsatile dynamics of fetal vessel walls, and the method suggests the possibility of estimating changes in the contractility of the fetal heart and the afterload in the fetal circulation.

Key words: Maternal smoking, pulse waves, fetal aorta

Cigarette smoking in humans produces several wellknown cardiovascular effects. In adults, a transient increase in heart rate, cardiac output, and arterial blood pressure has been found (1) as well as a shortened pre-ejection period and an increased venous return (2). Habitual smoking among pregnant women is still common in spite of anti-smoking campaigns (3). The chronic effects of maternal smoking on the fetus are well documented (3) but the acute fetal responses to smoking are not understood. Recording of the fetal heart rate (FHR) has revealed a transient elevation of the basal heart rate (4) together with a decrease in heart rate variability (5,6).

Introduction of the ultrasonic real-time B-mode technique has opened up new perspectives for non-invasive examination of fetal dynamics in utero. Thus, the fetal cardiac geometry has been investigated by means of M-mode echocardiography (7) and, by combining real-time ultrasonography and pulsed Doppler ultrasound, it has become possible to measure the blood flow in the fetal central vessels (8). A new phase-locking ultrasound system has proved competent for non-invasive measuring of pulsatile changes in arterial diameter (9). This method has a high spatial and temporal resolution (10) and has, after further developments, been used to characterize the physiological pulsations in the descending aorta of the human fetus in utero (11).

The purpose of the present study was to test the reactivity of the fetal cardiovascular system and to measure some acute responses to maternal cigarette smoking in the last trimester of normal gestation by quantitative monitoring of the pulsations of the fetal aorta.

Material and Methods

Seventeen healthy pregnant women of median age 28 (range

22-39) years participated in the study after giving informed consent. All fetuses showed a normal growth profile, as estimated by ultrasonography in the 17th and 33rd week. At the time of the investigation (gestational age 33-37 weeks) the fetuses were still normal, according to routine clinical criteria. Median gestational age at parturition was 40 weeks (range 34-41 weeks) and the median birth weight was 3010 g (range 2130-3480 g). None of the infants was distressed during birth.

All women had been smoking for several years and had a median daily consumption of 10 cigarettes (range 5-20 cigarettes) during the present pregnancy. The women were urged to abstain from smoking for 12 hours prior to the study and were recumbent, tilted slightly to the left, throughout the study. Only recordings indicating that the fetus was in a resting state and without fetal breathing and gross movements were accepted.

Eleven fetuses were investigated only once, in association with exposure to maternal smoking. In order to study the influence on these variables of the urge to smoke caused by the nicotine abstinence, 6 women were subjected to a repeat study. This part of the study was performed on two successive days in a single-blind, randomized order: one day the women smoked during the test as described below; the other day she did not (to her surprise) receive a cigarette but otherwise the same procedure was followed.

The investigation was started with three control recordings at -10 min, -5 min, and 0 min. After the third control measurement, starting at zero hours, the women smoked one cigarette with an average content of 1.6 mg nicotine (manufacturer's statement). From the onset of smoking the study proceeded for a further 45 min with recordings at +3 min, +5 min and thereafter every 5 min. Free-flowing blood for the determining of maternal carboxy-

hemoglobin (CoHb) percentage and nicotine concentration was collected via an indwelling cannula in an antecubital vein at -10 min, +10 min, and +45 min. Nicotine was measured by a method comprising gas-liquid chromatography and mass-spectrometry, with an intra-assay coefficient of variation of 7.0% (12).

A longitudinal ultrasound section of the fetal descending aorta was visualized on the screen of a real-time scanner (ADR, Tempe, Arizona) fitted with a linear array 3.0 MHz transducer. Diameter pulse signals were obtained from the fetal aorta with a specially designed electronic echo-tracking instrument (Diamove 820, Teltec, Lund, Sweden (10)). The echo-follower tracked the movements along the axis of the ultrasound beam of two aortic walls, yielding an output differential signal representing the instantaneous vessel diameter. At a depth of 10 cm, the repetition frequency of the measurement was 2.56 kHz with a maximal tracking velocity of 320 mm/sec and a minimum detectable movement in axial direction of 30 μm. The measuring cycles of the echo-tracking system were interspersed between imaging cycles, allowing a close surveillance of the fetus throughout the recordings. An electronic signal for calibrating of the diameter was inserted after every recording. Fetal ECG was obtained simultaneously via external electrodes.

The output signals from the phase-locking instrument were stored on magnetic tape and later replayed on a chart recorder with a speed of 200 mm/sec. A microcomputer was used for off-line analog-to-digital conversion of the pulse curves. Average data of 10 well defined pulse curves were calculated in each measurement. The following parameters of the diameter pulse curve were obtained: the apparent diastolic diameter, the pulse amplitude, the propagation time, the inclination time, the maximum

Table I. Parameters for description of the pulse wave curve

Variable	Definition	Number of	Denomination
Apparent diastolic diameter	Minimum diameter measured at the onset of the cycle, i.e. close to but exceeding the internal calibre of the vessel	15	mm
Pulse amplitude	Maximum increment of the diameter	17	mm
Propagation time	Interval from onset of Q-wave to foot of the pulse wave	11	msec
Inclination time (absolute or relative)	Length on time axis of a tangent to steep part of ascending leg between the intercepts with the base level and the peak level, respectively	17	msec or percentage of cycle
Maximum increment velocity	Maximum slope of ascending leg	17	mm/sec
Late decremental velocity	Maximum slope of last part of descending leg	15	mm/sec

increment velocity, and the late decremental velocity. In order to evaluate whether a change of the last three parameters was secondary to change in FHR, the inclination time was also expressed in per cent of the pulse length, and the two velocities were also given as values normalized to a FHR of 120 beats per min assuming a symmetrical

change in the curve. The definition and denominations of the parameters are given in Table I. As in each vessel wall the echo-tracking system locked to echoes from structures at a small distance outside the blood-intimal border, the "apparent diastolic diameter" denotes a value slightly exceeding the internal calibre of the vessel.

Non-parametrical statistics were used. The results are given as median and range values. Wilcoxon's test for pair differences was chosen as the statistical method. To calculate correlation coefficients, Spearman's rank correlation coefficient was used. A probability of 5% was adopted as the limit of significance.

RESULTS

Recording of the diameter pulses yielded technically acceptable signals in 253 out of 299 measurements in the 17 fetuses. The failure rate of 15.4% was due to the lack of a stable picture of the fetal descending aorta within the tight time schedule because of concomitant fetal breathing or fetal gross movements.

The COHb percentage in the total group rose from 0.52% (range 0.21-1.34%) to 1.42% (range 0.29-2.09%) at +10 min ($p < 0.01$) and remained elevated to 1.23% (range 0.71-2.39%) at +45 min ($p < 0.01$). In the randomized study the initial values were 0.69% (range 0.44-1.06%) on the control day and 0.72% (range 0.21-1.34%) on the day of smoking a cigarette. At +10 min and +45 min after commencing smoking the COHb had risen to 1.49% (range 0.29-1.99%) ($p < 0.05$) and 1.44% (range 1.11-2.39%) ($p < 0.05$), respectively, while the COHb percentage did not change significantly on the control day. The median basal nicotine concentration before smoking was <2 ng/ml (range <2-5 ng/ml). Ten min after starting smoking the concentration had increased to 21 ng/ml (range 6-40 ng/ml) ($p<0.01$) and

45 min after the onset the concentration had dropped to 5 ng/ml (range <2-16 ng/ml). In the randomized part of the study the median concentrations at -10 min, +10 min, and +45 min were <2 ng/ml (range <2-3 ng/ml), 16 ng/ml (range 10-40 ng/ml) ($p < 0.05$), and 4 ng/ml (range <2-14 ng/ml), respectively the day of smoking, while no changes in the concentrations were found on the smoking-free day.

Table II. Maternal and fetal heart rates before and after smoking one cigarette.

Time (min.)	-10	-5	0	3	5	10	15	20	25	30	35	40	45
Maternal heart rate, beats/min.													
Median	77	79	77	109^{++}	112^{++}	108^{++}	100^{++}	90^{++}	88^{+}	83^{+}	82	91	84
Minimum	65	63	59	94	83	76	60	65	63	60	61	59	65
Maximum	110	100	100	140	145	134	120	105	107	110	110	110	126
Fetal heart rate, beats/min.													
Median	139	138	137	141	155^{++}	152^{++}	146^{++}	138	138^{+}	136	138	142	143
Minimum	121	118	114	128	133	132	120	118	124	112	117	126	117
Maximum	154	154	159	160	172	171	160	160	166	162	164	156	160

+ $p < .05$ ++ $p < .01$

A. Entire group

The maternal heart rate increased by 42.1% from 79 beats/ min within 3 min after the onset of smoking ($p < 0.01$) and was still significantly elevated after 30 min. The fetal heart rate rose from an initial value of 138 beats/ min by 14.0% ($p < 0.01$) at +5 min and had returned to the control

Table III. Fetal circulatory parameters in the abdominal aorta before and after smoking.

Time (min)	-10	-5	0	3	5	10	15	20	25	30	35	40	45
Diastolic diameter, mm													
Median	5.9	5.9	5.9	6.5	6.2^{++}	6.3^{+}	6.2^{+}	5.9	5.9	6.1	5.9	6.1	6.1
Minimum	4.8	4.9	4.5	4.6	5.0	5.1	5.4	4.5	4.7	5.5	4.8	4.8	4.8
Maximum	7.5	6.8	6.5	7.6	7.0	7.1	7.0	7.5	6.8	7.4	7.0	6.8	7.2
Pulse amplitude, mm													
Median	0.94	1.00	0.99	1.03	1.00^{+}	1.03^{++}	0.98^{++}	1.08^{++}	1.03	1.04	1.01	0.96	1.01
Minimum	0.53	0.64	0.64	0.70	0.69	0.75	0.66	0.70	0.58	0.68	0.72	0.68	0.64
Maximum	1.13	1.17	1.15	1.19	1.26	1.29	1.34	1.39	1.41	1.15	1.44	1.23	1.12
Pulse propagation time, msec													
Median	77.6	77.6	78.1	73.4	70.1^{++}	69.0^{++}	72.3^{++}	73.3^{++}	73.8^{+}	75.3	75.3	77.4	76.5
Minimum	64.7	66.1	65.0	63.4	60.0	59.0	65.3	61.7	62.8	66.3	63.3	62.8	62.9
Maximum	84.8	83.2	89.6	90.7	85.4	81.9	80.0	84.6	81.4	80.9	92.9	86.7	83.5

+ $p < .05$ ++ $p < 0.1$

Table IV. Form analysis of the diameter pulse curve in the fetal descending aorta before and after maternal smoking.

Time (min)	-10	-5	0	3	5	10	15	20	25	30	35	40	45
Inclination time, msec													
Median	49.5	49.6	49.2	47.2^{+}	41.7^{++}	39.4^{++}	42.6^{++}	45.3	46.9	51.2	45.5	47.8	48.6
Minimum	36.2	37.4	33.9	33.2	30.9	30.2	29.3	37.1	36.1	33.1	37.9	36.7	36.6
Maximum	59.7	63.6	62.1	55.6	53.2	49.3	46.8	55.6	57.7	57.9	56.3	55.7	53.3
Relative Inclination time, %													
Median	11.5	11.3	11.5	11.3	10.8^{++}	10.0^{++}	10.2^{++}	10.5	11.4	11.4	10.7	11.1	11.2
Minimum	9.2	8.7	7.6	7.8	8.2	7.6	7.1	8.5	8.6	8.5	8.0	9.1	8.9
Maximum	13.2	13.4	14.3	12.8	12.5	12.3	12.4	12.7	13.0	12.2	12.0	12.4	12.3

+ $p < .05$ ++ $p < .01$

values at +20 min (Table II). The FHR at +10 min and the difference in heart rates between the periods -10 min and +10 min were positively correlated to the nicotine concentration at +10 min ($R = 0.71$, $p < 0.01$) and to the difference in the nicotine concentrations between the periods -10 min and +10 min ($R = 0.59$, $p < 0.05$), respectively. No other correlations were found between the nicotine concentration or the change in concentration and the various parameters used in the study. The initial levels of COHb, its levels at +10 min, and the increments of the COHb were not correlated to any variables recorded at -10 min and +10 min, or to the changes in any of the variables between these two times.

The apparent diastolic aortic diameter before smoking was 5.9 mm, increasing by 11.6% in the period +5 to +15 min ($p < 0.01$). The pulse amplitude was found to increase from 0.98 mm in the control period by 13.8% from 5 to 20 min after starting smoking ($p < 0.01$) (Table III). The pulse propagation time to the level of the diaphragm was 77.7 msec and was found to decrease from 5 to 25 min after smoking by 11.5% ($p < 0.01$) (Table III). The waveform of the diameter pulse curve changed in several respects after smoking. The duration of the first ascending part of the pulse curve - the inclination time - was 49.5 msec before smoking, and it was significantly reduced during the time +5 min to +15 min by 20.2% ($p < 0.01$). The relative inclination time also declined significantly, by 17.1% from 5 to 15 min after starting smoking, from an initial value of 11.5% of the total cycle length ($p < 0.01$) (Table IV).

The maximum increment velocity increased within the first 15 min after smoking from 20.2 mm/sec by up to 26.7% ($p < 0.01$). The late decremental velocity decreased by a maximum of 23.2% within 20 min after starting smoking, from an initial value of 2.53 mm/sec. Even when these two last parameters were normalized with regard to the FHR,

significant changes after smoking were found (Table V and VI).

Table V. Form analysis of the diameter pulse curve in the fetal descending aorta before and after maternal smoking.

Time (min)	-10	-5	0	3	5	10	15	20	25	30	35	40	45
Maximum Increment velocity, mm/sec													
Median	19.0	20.4	20.2	20.9	23.3^{++}	25.7^{++}	24.3^{++}	21.0	20.9	21.6	22.3	20.9	20.1
Minimum	14.5	15.3	14.0	16.2	16.6	15.6	15.2	15.4	12.7	15.1	16.2	16.5	15.0
Maximum	25.6	23.2	26.0	25.2	28.1	30.3	26.8	26.9	24.9	25.5	25.6	25.3	27.3
Maximum Increment velocity, mm/sec normalized to FHR 120 beats/min													
Median	14.4	15.0	14.9	14.9	15.7^{+}	15.9^{++}	15.8^{++}	14.9	15.3	15.6	16.4	15.2	14.5
Minimum	10.0	9.9	8.8	10.5	10.6	9.1	9.6	11.3	8.2	10.6	11.1	10.8	10.0
Maximum	20.6	18.4	19.4	19.4	19.0	20.2	21.0	20.2	18.4	17.1	19.3	18.7	19.8

+ $p < .05$ ++ $p < .01$

Table VI. Form analysis of the diameter pulse curve in the fetal descending aorta before and after smoking.

Time (min)	-10	-5	0	3	5	10	15	20	25	30	35	40	45
Late decremental velocity, mm/sec													
Median	2.53	2.49	2.59	2.31^{+}	2.14^{++}	2.07^{++}	2.08^{++}	2.41	2.44	2.47	2.46	2.73	2.50
Minimum	1.66	1.49	1.68	0.87	1.04	1.01	1.52	1.60	1.60	1.41	1.53	1.50	1.62
Maximum	3.39	3.60	3.12	2.84	2.74	2.88	2.70	3.12	3.01	3.17	3.08	3.30	3.16
Late decremental velocity, mm/sec normalized to FHR 120 beats/min													
Median	2.26	2.17	2.27	1.97^{+}	1.72^{++}	1.62^{++}	1.70^{++}	2.01	2.07	2.04	2.49	2.30	2.10
Minimum	1.29	1.30	1.50	0.80	0.91	0.86	1.15	1.11	1.11	1.33	1.38	1.29	1.40
Maximum	3.09	3.43	3.11	2.40	2.38	2.16	2.55	2.97	2.74	3.02	2.94	3.14	2.92

+ $p < .05$ ++ $p < .01$

B. Repeat study group

The 6 cases which were studied twice in the randomized part of the investigation showed an increase in both fetal and maternal heart rate on the day of smoking ($p < 0.05$), whereas no significant changes in the heart rates were noted on the control day (Fig. 1). The pulse amplitude during the control period on the smoking day did not differ from that on the control day. The amplitude increased by a maximum of 15.8% from 0.88 mm ($p < 0.05$) after smoking, while no changes were found on the non-smoking day. The inclination time decreased within 5 to 10 min after smoking by a peak value of 18.2% from a control level of 47.1 msec ($p < 0.05$). The maximum increment

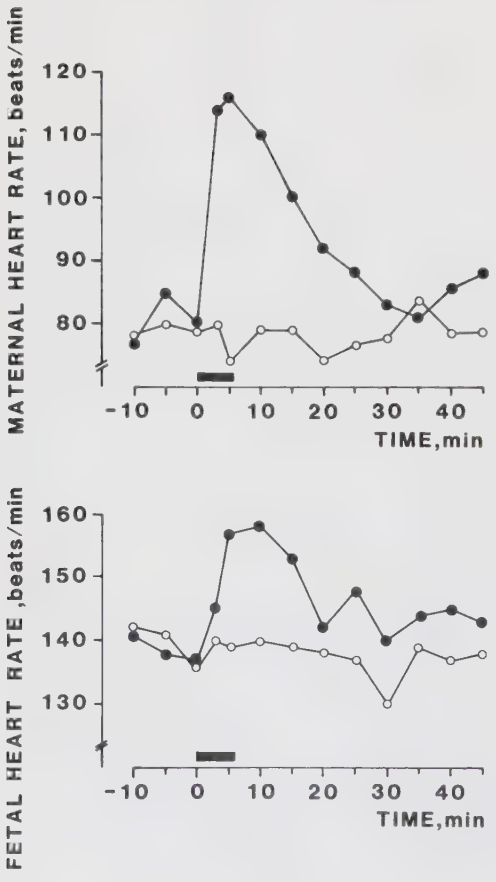

Fig. 1 The maternal (upper picture) and the fetal (lower picture) heart rate in relation to time. Filled circles denote heart rates during smoking test, open circles denote heart rates during non-smoking control test. Filled bar indicates the time of smoking.

velocity rose from 18.1 mm/sec 5 to 10 min after smoking y a maximum of 21.6% ($p < 0.05$). There was a decrease in the late decremental velocity with a maximum value of 30.2% from 2.14 mm/sec 5 to 10 min after the start of smoking ($p < 0.05$). No statistically significant change in either parameter was seen on the control day.

DISCUSSION

The observation in the present study that the parameter changes in all the fetuses occurred in the same direction indicates the use of the ultrasound system to quantify the responses of the fetal circulatory system to certain external stimuli, such as maternal smoking. A success rate of 84.6% was achieved in obtaining at least 10 technically acceptable pulse curves for each scheduled period in the study. This was a highly satisfactory result considering that for each recording only 4-5 min were available, and that during approximately 40% of the day the human fetus reportedly breathes or performs gross movements (13) which render the recordings invalid for the present purpose. The high sensitivity and specificity of the measurements of the pulsatile diameter changes in the fetal aorta have been documented earlier (10,11), the latter quality is to a large extent dependent on the freedom in the system from restrictions to the movements. In all the pre-smoking control periods and during the non-smoking tests in the randomized part of the study no trend change was observed in any parameter. The randomized study was conducted "blind" in order to investigate any effects of maternal apprehension or supine posture on the fetal pulse waves, but no such influence was detected in any of the cases.

The initial values of the COHb and the nicotine concentration in blood were within the range found for non-smoking women. Smoking induced a rapid and parallel elevation of the maternal heart rate, the COHb, and of the nicotine

concentrations. The magnitude and the duration of the increments induced by smoking in this study were very similar to those found in man when smoking one high--nicotine content cigarette (2) or in pregnant women smoking two standard cigarettes (4). The response of the FHR to maternal smoking, with a maximum increase in the median level of 14%, was consistent with observations in earlier reports (4,5). The change in the FHR, however, was less than the increase in maternal heart rate. Moreover, the increase in the maternal heart rate preceded that of the FHR by 3-5 min. The difference may be due to the transit time of vasoactive agents from the tobacco smoke across the placenta and/or the latency time after any circulatory disturbance in the uterus.

The waveform of the diameter pulse in the fetal aorta changed markedly after maternal smoking, as is evident in Fig. 2. The pulsatile amplitude of the diameter increased; as an expansion of the diastolic diameter was also found, the volume capacity of the aorta seemed to have risen markedly (by approximately 27%). The incremental slope of the pulse curve became steeper, and the late decremental phase turned into a more gentle slope. The former change might have been secondary to the concomitant shortening of the pulse cycle during the increased FHR, but the increase in the slope exceeded the value caused by a symmetrical compression of the curve along the time axis. Moreover, the decrease in the relative inclination time by nearly the same magnitude as the decrease in the absolute inclination time suggest that the major part of this change was caused by the cigarette smoking and not by the change in the FHR *per se*. The alteration in the late decremental phase was directionally contrary to the change expected from an increased FHR.

The fact that smoking via nicotine activates the adrenergic system, makes the fetal circulation the target of a

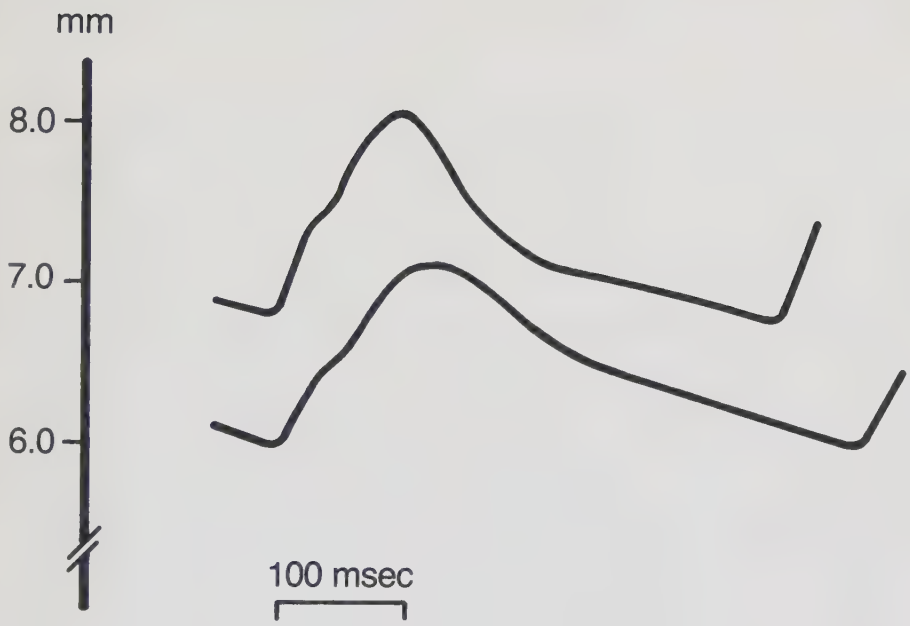

Fig. 2 Diameter pulse curves (patient I.H., 37th gestational week) averaged from ten consecutive pulse cycles 10 min before (lower trace) and 10 min after (upper trace) the onset of maternal smoking. The lowest level of each trace denotes the apparent diastolic diameter.

series of complex effects. Both when nicotine is transferred across the placenta, causing a release of noradrenalin directly in the fetus, and when a nicotine-induced constraint on the placental perfusion elicits fetal hypoxia, vasoactive effects on the fetal aorta have to be considered. It has been demonstrated in animal experiments that both infusion of noradrenalin (14,15) and activation of the adrenergic system by bleeding (16)

produce a constriction of the ascending and the descending aorta. These constrictions, however, were of a smaller amplitude than the relaxation of the aorta caused by injection of an alpha-blocking agent (15), suggesting that there is a high resting tone in the muscular coat of the aorta.

The effect on the width of the aorta caused by administration of nicotine and/or production of hypoxia probably results from two opposing forces. The catecholamine--induced contraction of the aortic wall will be counteracted by the dilatation due to an increased peripheral resistance, with an increased intravascular pressure. Such a balance is also illustrated by the unchanged pressure-strain elastic modulus compared at equal pressures before and after noradrenalin-induced contraction of the aortic smooth muscle (15). This absent response has been ascribed to the combined action of the muscular contraction making the aortic wall more rigid and the reduced tension due to the somewhat diminished vessel radius increasing the compliance of the wall (15).

It is difficult from the findings in the present study to separate two opposing effects on the aorta exerted by any activation of the adrenergic system. The increase in the diastolic diameter suggests a higher post-smoking distending force with increased intravascular pressure caused, for example, by a rise in the peripheral resistance. The appearance of increased peripheral resistance is corroborated by the reduced late decremental velocity of the pulse wave. As the propagation velocity of the pulse over a given segment of the fetal aorta was not measured in the study, it is an open question whether the shortened pulse propagation time after smoking was caused at least partly by an increased pulse propagation velocity (see below). If the velocity were raised, this would support the earlier observation that vasoconstricting agents cause a rise in

the wave-velocity in the aorta (17). The finding in rabbits that the pressure response to catecholamine infusion preceded the constriction of the aorta by 2-3 min (15) could, unfortunately, not be used to distinguish between the two effects in the present investigation, because of widely scattered time courses.

The pre-ejection period (PEP) was not calculated but, judging from earlier measurements of this electromechanical interval (18), it is obvious, however, that the PEP constitutes the major part of the propagation time measured here, and also that the predominant changes in the propagation time must originate from variations in the PEP. In several studies on the fetus the PEP has been found to decrease in response to acute hypoxia (18). Cigarette smoking has been claimed to cause acute fetal hypoxia via uterine vasoconstriction and a diminished uteroplacental perfusion (4). Release of catecholamines by nicotine will lead to increased myocardial contractility and a shortening of the PEP (18). A concomitant chemoreceptor-induced peripheral vasoconstriction causes a rise in the arterial blood pressure and a fall in the heart rate, contrary to the increase in the fetal heart rate found in this study. The shortened electromechanical interval can therefore not be taken as an absolute sign of fetal hypoxia. In fact, no indices of fetal compromise were observed recently in cardiotocograms from healthy fetuses recorded up to one hour after maternal smoking (5).

The present observations of a shallower late decremental slope of the pulse wave and an increased apparent diastolic diameter suggest an increased afterload in the fetal circulation appearing after maternal smoking. Tobacco smoking in human has also been found to increase the maternal arterial blood pressure during pregnancy (4), but there were no signs in the present study that increased

fetal blood pressure affected the compliance of the fetal aortic wall. In arteriosclerotic vessels for instance, the inclination time has been found to be prolonged and the systolic slope to be reduced (19). By contrast, maternal smoking induced a decreased inclination time and an increased maximum increment velocity in the fetal aorta. These observations, as well as the increased pulse amplitude, seem to reflect a positive inotropic effect leading to an enhanced myocardial contractility in the fetus. As the Frank-Starling effect has been shown to apply also to the fetal heart (10,20,21) it is pertinent to note that the signs of increased fetal cardiac output after maternal smoking appeared despite any negative effect on the filling of the heart ventricles caused by the increased FHR.

In conclusion, by using real-time ultrasound in combination with a phase-locking echo-follower we have demonstrated changes in the fetal cardiovascular system after maternal smoking. It appears that smoking induces changes in the fetal circulation similar to those found in adult humans, i.e. an increased afterload and an enhanced contractility of the fetal myocardium. No signs of fetal hypoxia were found. Some of the parameters of the pulse curve from the fetal aorta, viz. inclination time, maximum increment velocity, and late decremental slope, may serve as useful indicators of the condition of the fetal cardiovascular system.

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ACUTE EFFECTS OF MATERNAL SMOKING ON FETAL BLOOD FLOW

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ABSTRACT

Thirty healthy pregnant women were studied to assess the immediate cardiovascular responses of the fetus to the smoking of one cigarette. The fetal blood flow was measured in the aorta and in the umbilical vein by combining real-time ultrasonography and the pulsed Doppler technique. Following maternal smoking, a significant increase was found in the maternal heart rate and also in the blood pressure. In the fetus, a significant transient increase in the aortic and the umbilical blood flow was measured, as characterized by the increase in the fetal heart rate, the mean and maximum blood velocity, and the vessel diameter. Thus, maternal smoking induced acute circulatory changes in the fetus similar to those found in adults. Furthermore, the study demonstrated the feasibility of the method to evaluate non-invasively the immediate effect of a given stress stimulus on the cardiovascular system of the human fetus.

Key words: Maternal smoking, fetal blood flow, pulsed Doppler ultrasound.

INTRODUCTION

Two important factors in maintaining intra-uterine life are the intervillous and the fetal blood flow. Studies on chronic animal preparations have hitherto been the main source of our information on antenatal cardiovascular circulation. The progress achieved in the field of diagnostic ultrasonography has opened up new perspectives for non-invasive studies on human fetal circulation in utero. By combining real-time ultrasonography and pulsed Doppler ultrasound it has become possible to measure the blood flow in the descending aorta and umbilical vein of the human fetus in the second half of gestation (2). The method has proved valuable in measuring fetal blood flow under physiological conditions as well as under pathological circumstances, e.g. in cardiac arrhythmia (9).

Maternal smoking has been shown to exert an immediate depressive effect on the placental blood flow (5), but the acute fetal cardiovascular responses to smoking are still poorly understood. A transient elevation in fetal heart rate has been observed (12) with a comcomitant decrease in heart rate variability (16).

The purpose of the present study was to evaluate conceivable immediate effects on the fetal blood flow after maternal smoking of one cigarette in the last trimester of normal gestation.

MATERIAL AND METHODS

The study was performed on 30 healthy pregnant women with a median age of 27.5 (range 21-39) years in the 31st to 40th week of gestation (median 36 weeks). Gestational age was estimated by ultrasound fetometry in the 17th week. All women were habitual smokers, whose median daily consumption during pregnancy was 13 (range 5-20) cigarettes. All agreed to participate in the investigation after being informed about its purpose. The pregnancies were

normal at the time of the investigation, according to routine clinical criteria. At parturition subsequently, median gestational age was 40 (range 37-42) weeks and median birth weight was 3 265 (range 2 600-4 180) g. Apgar scores at 1 and 5 min were in the range 7-9 and 9-10, respectively.

The women were urged not to smoke for at least 12 hours prior to the study. During recording, the women lay recumbent in a left-tilted position. Only recordings with the fetus in a resting state, i.e. without gross fetal movements or fetal breathing movements, were accepted. The time schedule for the investigation is shown in Fig. 1.

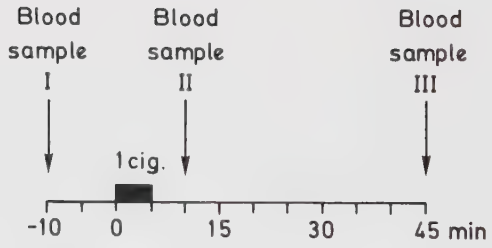

Fig. 1
Time schedule of the investigation. Registration. Registrations were made every 5 min, starting with three control measurements.

After 15 minutes for settling down, the study began with a 10-minute control period. Then the women smoked one cigarette yielding 1.6 mg nicotine (the manufacturer's statement) and the study proceeded for a further 45 min from the onset of smoking.

Blood flow measurements were performed in 20 of the fetuses in the descending aorta (Aorta group). In 6 of these fetuses the investigation was done on two subsequent days in a randomized order with or without the smoking. In the other 14 instances the investigations were performed with smoking only. Measurements of the following parameters were made at 5-minute intervals: maternal heart rate and blood pressure, fetal heart rate counted from the blood velocity traces, diameter of the fetal descending aorta, mean blood velocity, maximum peak blood velocity and mean aortic blood flow. Free flowing blood for the determination of carboxyhemoglobin (COHb) percentage and nicotine concentration was collected from an indwelling cannula in an antecubital vein at -10 min, +10 min, and +45 min. The nicotine was measured with a method comprising gas-liquid chromatography and mass-spectrometry with an intra-assay coefficient of variation of 7%.

In the remaining 10 fetuses the measurements were performed in the intra-abdominal part of the umbilical vein (Umbilical vein group) before and after maternal smoking according to the same schedule (Fig. 1). No blood samples were taken in this group. The maternal parameters were the same as in the aortic group. The fetal parameters were: heart rate, diameter of the umbilical vein, mean blood velocity, and mean umbilical blood flow.

The measurement of the blood flow in the abdominal aorta and the intra-abdominal part of the umbilical vein was accomplished by the combination of a real-time scanner (ADR 3020, Tempe, Arizona; 3.5 MHz) and a pulsed Doppler

instrument (ALFRED, Vingmed, Oslo, Norway; 2.0 MHz). The real-time scanner was calibrated to the velocity of sound 1 540 $m.s^{-1}$. To remove signals from slow moving tissues in the path of the beam, a 400 Hz high-pass filter was used in the first 10 investigations in the aortic group, while a 100 Hz filter was chosen in all the other investigations.

Fetal blood flow was measured by a method described by Eik-Nes and associates (2). The Doppler transducer was attached to the real-time transducer at a fixed angle of 45^{o}. Either fetal aorta or the umbilical vein was visualized on the B-mode screen. The real-time transducer was moved until it was positioned parallel to the vessel's longitudinal axis. In this position the angle between the Doppler beam and the vessel was known (45^{o}), enabling correction of the recorded blood velocity for the angle. The sample volume of the Doppler velocity meter was adjusted to the correct position and Doppler signals of the blood flow recorded. The calculation of blood velocity at each registration was based on traces of at least 15 s duration under steady state conditions. The vessel diameter was measured using a TD-recorder (2,8). Vessel cross-sectional area (A), assumed to be circular, was calculated from the diameter. The blood flow (Q) was calculated according to the formula $Q = V.A.\cos 45^{o-1}$. The blood flow was related to the fetal weight estimated from the sonically measured biparietal and abdominal diameters and expressed in $ml.min^{-1}.kg^{-1}$.

Non-parametric statistics were used: The results were expressed as median and range values ; Wilcoxon's test for paired observations and Spearman's rank correlation test were the chosen methods for the statistical calculation. Five per cent was adopted as the level of significance.

RESULTS

Aorta group

Measurement of blood flow in the descending aorta of the 20 fetuses was successful in 278 out of 312 registrations. 18.9% of the recordings had to be rejected because of gross fetal movements or fetal breathing movements.

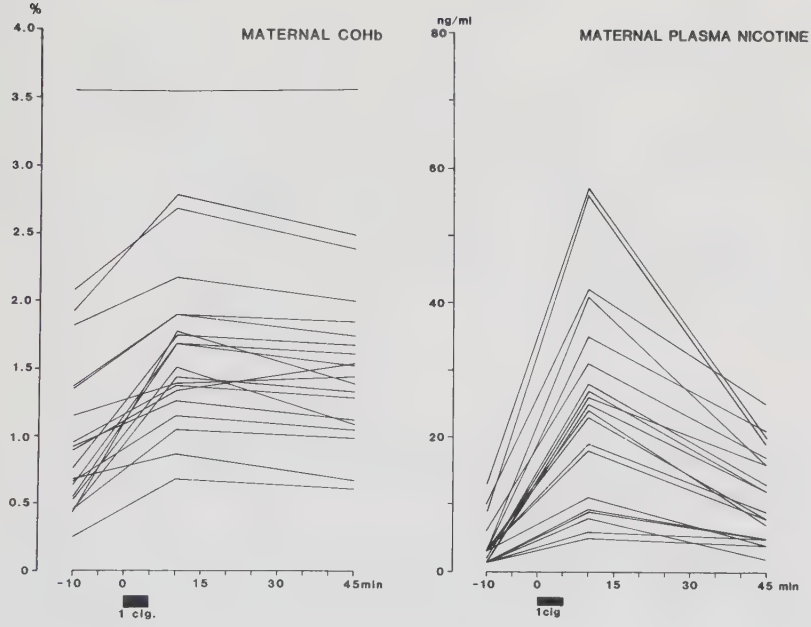

Fig.2

COHb percentages and nicotine concentrations in maternal blood before and after the smoking of one cigarette (Aorta group, n=20).

The median COHb percentage rose from 0.92% to 1.60% 10 min after the onset of smoking ($p<0.01$) and then decreased to 1.49% 35 min later (Fig. 2). In the randomized control

study (n=6), the median COHb concentration changed from 0.63% to 1.27% at +10 min ($p<0.05$) and to 1.10% at +45 min on the day of smoking, whereas the COHb concentration fell slightly throughout the investigation on the control day without smoking, from 0.94% at -10 min to 0.83% at +45 min.

The basal nicotine concentrations in the maternal blood prior to smoking ranged from <2 to 13 (median <2) $ng.ml^{-1}$. Ten min after the onset of smoking, the nicotine concentration increased to a median of 26 $ng.ml^{-1}$ and decreased to 8 $ng.ml^{-1}$ at +45 min (Fig. 2). In the randomized part of the study, the median nicotine concentration increased from <2 $ng.ml^{-1}$ to 16 $ng.ml^{-1}$ at +10 min and to 6 $ng.ml^{-1}$ at +45 min on the day of smoking, while no significant changes in nicotine concentration were found on the control day.

Table I. Maternal circulatory parameters in 20 normal pregnant women before and after smoking (Aorta group; smoking time 0-5 min).

Time (min)	-10	-5	0	5	10	15	20	25	30	35	40	45
Heart rate (beats/min)												
Median	84	88	84	108**	104**	100**	96**	96**	96**	92**	90**	92**
Range	66	64	68	84	84	80	78	76	80	80	76	76
	104	100	100	132	124	132	114	120	120	104	120	124
Systolic blood pressure (mm Hg)												
Median	110	105	108	125**	120**	115**	113**	110**	110	110	110	110
Range	100	100	100	115	110	110	100	100	95	100	100	100
	130	130	130	130	140	135	130	130	130	130	130	130
Diastolic blood pressure (mm Hg)												
Median	70	70	70	80**	80**	75**	73**	70**	70	70	70	70
Range	60	60	60	75	70	65	65	65	65	60	65	60
	80	85	85	85	85	85	85	80	80	80	80	80

* $p< 0.05$; ** $p< 0.01$

The maternal and fetal circulatory parameters are given in Tables I and II. The median maternal heart rate rose from 84 beats.min^{-1} by a maximum increase of 29.5% 5 min after the onset of smoking and was still significantly different from the control values after 45 min. The maternal systolic and diastolic blood pressures increased from the median values of 108 mmHg and 70 mmHg, respectively, by maximum increases of 12.5% and 14.0%, respectively. 25 min after the onset of smoking both the systolic and the diastolic blood pressure had returned to the control levels. The median fetal heart rate increased from a control value of 136 beats.min^{-1} by a maximum increase of 13.0% during the period 5 to 25 min after the onset of smoking. The median fetal aortic diameter before smoking was 6.6 mm, increasing by a maximum of 5.1% during the first 15 min following the smoking. Within the same period there was a maximum rise in the peak blood velocity of 14.7% from a median value of 95.2 cm.s^{-1}. In the 10

Table II. Fetal circulatory parameters in 20 pregnancies before and after smoking (Aorta group; smoking time 0-5 min).

Time (min)	-10	-5	0	5	10	15	20	25	30	35	40	45
Heart rate (beats/min)												
Median	136	136	140	148**	152**	150**	144**	140*	144*	144*	144*	144
Range	116	116	114	124	132	128	126	120	124	114	126	112
	168	164	160	184	192	204	210	184	179	172	180	172
Mean aortic diameter (mm)												
Median	6.6	6.5	6.6	6.9**	6.9**	6.8**	6.6	6.7	6.7	6.7	6.7	6.6
Range	5.8	5.7	5.6	5.9	5.8	5.7	5.9	5.8	5.6	5.8	5.5	5.8
	7.9	8.0	8.0	8.3	8.6	8.3	8.3	8.2	7.4	7.8	7.5	8.0
Peak maximum blood velocity (cm/s)												
Median	89.9	96.1	95.2	103.6**	105.3**	104.2**	95.7	101.2	94.7	95.4	95.4	89.7
Range	71.6	75.9	69.8	84.5	73.9	73.7	75.6	71.7	74.1	72.3	74.7	72.2
	128.8	125.4	119.7	164.6	166.1	179.0	141.1	135.6	140.6	130.1	132.2	123.6

* $p < 0.05$; ** $p < 0.01$

investigations where the 100Hz high-pass filter was used we found maximum rises in both the mean blood velocity and the mean aortic blood flow of 20.2% and 29.6%, respectively (Table III).

Table III. Results of blood flow measurements in the descending aorta of 10 fetuses before and after smoking (smoking time 0-5 min). Aorta group; only measurements performed using 100 Hz high-pass filter are included.

Time (min)	-10	-5	0	5	10	15	20	25	30	35	40	45
Mean velocity (cm/s)												
Median	27.8	30.1	25.7	32.0*	32.0**	29.7	27.6	29.6	25.7	29.2	28.3	27.5
Range	17.4	22.9	21.0	20.5	23.8	21.0	20.4	24.2	17.3	17.6	17.9	22.9
	43.4	41.0	38.9	49.9	45.9	47.8	46.9	43.5	39.9	41.6	43.4	44.7
Mean aortic flow (ml/kg/min)												
Median	238	258	230	274*	293**	271*	267*	256	224	237	217	237
Range	168	198	194	197	247	195	196	219	158	146	160	181
	280	288	280	359	371	378	352	302	296	314	289	328

* $p < 0.05$; ** $p < 0.01$

The number of cigarettes consumed per day, the fetal heart rate, the various fetal flow parameters and the change in the aortic diameter were not correlated to the maternal levels of COHb and nicotine or to the change in COHb and nicotine after smoking.

In the randomized study no significant differences in any of the parameters were found between the control periods on the smoking and the non-smoking days. During the period 0 to 15 min there was a significant difference ($p<0.05$) in all circulatory parameters between the smoking day and the non-smoking day. The changes in the fetal heart rate and the mean aortic blood flow are illustrated in Fig. 3.

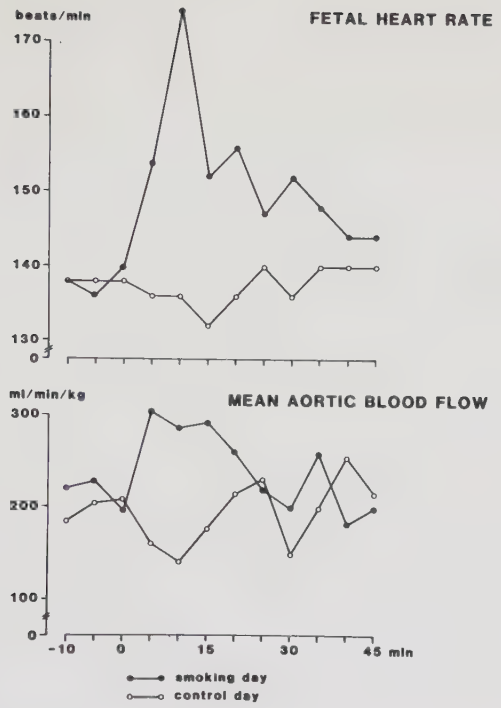

Fig. 3
Fetal heart rate and mean aortic blood flow in the randomized part of the study (n=6). One day the women smoked one cigarette (closed symbols); the other day an identical procedure was followed, except that the women did not smoke (open symbols).

Umbilical vein group

The recordings of the blood flow in the umbilical vein were successful in 82.5% of attempts, while there were 21 drop outs (out of 120 registrations) because of gross fetal movements, fetal breathing movements or fetal position.

The median maternal heart rate increased significantly from 82 beats. min^{-1} by a maximum of 30.5%, returning to

Table IV. Maternal circulatory parameters in 10 normal pregnant women before and after smoking (Umbilical vein group; smoking time 0-5 min)

Time (min)	-10	-5	0	5	10	15	20	25	30	35	40	45
Heart rate (beats/min)												
Median	82	82	84	96**	90*	92*	90**	96*	90*	88	84	86
Range	68	68	68	80	80	80	72	72	68	64	80	76
	104	102	108	136	128	124	124	116	124	112	112	116
Systolic blood pressure (mm HG)												
Median	110	108	106	118**	120**	115*	110	110	105	105	110	105
Range	95	95	95	110	105	105	100	100	100	95	95	95
	130	130	130	140	135	135	130	130	130	125	130	130
Diastolic blood pressure (mm Hg)												
Median	73	70	73	80**	80**	75*	75	70	70	75	73	70
Range	60	60	60	70	70	60	60	60	60	60	60	60
	85	80	80	100	90	90	95	80	80	80	90	85

* $p < 0.05$; ** $p < 0.01$

Table V. Fetal heart rate and the results of blood flow measurements in the umbilical vein in 10 pregnancies before and after smoking (Umbilical vein group; smoking time 0-5 min)

Time (min)	-10	-5	0	5	10	15	20	25	30	35	40	45
Heart rate (beats/min)												
Median	132	134	132	148*	148*	140	138	134	132	134	130	134
Range	120	120	120	132	128	124	128	124	120	128	128	128
	144	144	140	176	188	172	168	140	148	164	144	144
Umbilical vein diameter (mm)												
Median	8.0	8.0	8.0	8.4**	8.5**	8.6**	7.8*	8.2	8.5*	8.4*	8.2	8.1
Range	5.9	5.9	5.8	6.1	6.2	6.6	6.5	6.8	6.4	6.7	6.2	5.7
	8.8	8.6	8.6	9.1	9.1	9.0	8.7	9.0	8.8	9.0	8.7	8.8
Mean blood velocity (cm/s)												
Median	11.0	9.2	8.1	15.2	11.4	14.8	12.1	12.0	10.7	10.7	12.1	11.4
Range	7.1	6.9	6.6	7.3	7.2	13.1	9.5	8.8	6.5	8.3	9.3	7.5
	15.6	15.8	19.1	17.8	16.1	16.7	21.9	22.2	16.0	15.8	14.6	21.6
Mean umbilical flow (ml/kg/min)												
Median	107.0	85.9	94.0	172.7	145.1	185.3*	136.9*	122.6*	122.1	121.1	138.7	102.1
Range	63.6	60.0	64.1	96.9	96.5	115.2	97.1	101.5	85.9	88.5	94.5	76.2
	193.8	189.0	178.6	22.9	208.7	197.6	202.0	261.1	157.0	209.3	170.2	173.1

* $p < 0.05$; ** $p < 0.01$

control values at 35 min. Systolic and diastolic blood pressure were significantly increased during the first 15 min after the onset of smoking, by maximum increases of 10.6% and 14.3%, respectively (Table IV). The median fetal heart rate rose from 132 beats.min^{-1} by a maximum of 16.4%, the rise being sustained for 10 min. The mean blood velocity did not change significantly after smoking but the umbilical vein diameter increased by a maximum of 8.7% of the median control value of 8.0 mm. The mean umbilical blood flow rose from a median control value of 94 ml.min^{-1}.kg^{-1} by 38.5% 15 to 25 min after the onset of smoking (Table V).

DISCUSSION

The present experiments clearly demonstrate that it is possible with the present method to evaluate non-invasively the immediate effects of a given stress stimulus on the cardiovascular system of the human fetus. Following maternal smoking, a significant transient increase was found in the fetal aortic and the umbilical blood flow, characterized by the increase in fetal heart rate, mean and maximum blood velocity and vessel diameter.

The number of missing registrations of blood flow in the fetal aorta and the umbilical vein was within an acceptable range for maintaining the continuity in the measurements throughout the study. The percentages of drop-outs (18.9 for the Aorta group and 17.5 for the Umbilical vein group) fit well with the percentage of time the fetus spent making gross body movements and breathing movements during the corresponding time of the day (11).

The COHb percentage and the nicotine concentration were determined in the venous blood of the women in order to confirm that they had abstained from smoking before the study and to measure the strength of the stimulus. The initial values of the COHb percentage were with one

exception within the range of non-smoking women (6). The same was true for the nicotine concentrations, with no exceptions. The responses to smoking were similar in all women, with an approximately parallel rise in COHb and nicotine (Fig. 2).

The increase in the maternal heart rate by 26% was similar in magnitude and duration to that reported after smoking one high-nicotine cigarette (13) or two standard ones (12). The increases in both systolic and diastolic blood pressure by approximately 15% were in the same range as mentioned by others (12,13).

The response of the fetus to maternal smoking, with a maximum increase in the median heart rate of 14%, is similar to that found in the study by Quigley and associates (12) with a concomitant rise in maternal plasma norepinephrine and epinephrine concentrations. The duration of the fetal heart rate elevation (40 min) was somewhat longer than that found in an earlier study (16) but the response was of nearly the same duration as found by Quigley and colleagues (12).

Possible methodological errors in the measurements of the fetal blood flow by the combined real-time and pulsed Doppler ultrasound technique were evaluated by Eik-Nes and associates (2). The accuracy and reproducibility of the results were found satisfactory. In the present study possible errors were minimized thanks to the design of the investigation, whereby the fetuses served as their own controls.

The control values of the blood flow in the descending aorta were 21% higher in this study than those reported by Jouppila and associates (4) and 29% higher than the values of Eik-Nes and colleagues (2). This discrepancy is due mainly to the difference in the techniques used: in both

of the studies cited (2,4) high-pass filters of 600 Hz were used - as shown later, the filters could eliminate a considerable proportion of the diastolic flow, thus erroneously reducing the resulting mean aortic blood flow by as much as 30% (9). In consequence of the above-mentioned study (9), the high-pass filter in the present study was changed from 400 Hz to 100 Hz after the first 10 examinations in the Aorta group. Therefore, only the results for mean aortic blood flow obtained from the last 10 patients are considered. The maximum peak velocity, however, was not influenced by the high-pass filter of 400 Hz and therefore data from all 20 patients are presented. In a study by Maršál and associates (9) on normal pregnancies using the same technique as in this investigation, the basic levels of the flow parameters were very close to the values found here. In the umbilical vein the present control values were not significantly different from the values reported by Eik-Nes and colleagues (2).

In the study by Jouppila and associates (4) using an ultrasound technique similar to that in the present investigation, no difference was found in the aortic or the umbilical vein blood flow after maternal smoking. In their study (4), measurements of COHb and nicotine in the maternal plasma were not made and no significant changes were seen in the maternal heart rate or the fetal heart rate between the control period and the test period. This suggests that insufficient smoke inhalation might be responsible for the lack of response. Furthermore, the design of the study was different: measurements were only performed immediately after ceasing smoking.

Nicotine crosses the placenta rapidly (7,17). In the pregnant ewe, the fetal concentration was found to equilibrate with the maternal concentration after 5 min (7). In the fetus of the Rhesus monkey, a maximum nicotine concentration was recorded 16 min after intravenous administration

of nicotine to the mother (17). The changes in aortic blood flow found in the present investigation coincided interestingly with the above mentioned increase in nicotine concentration in the animal fetuses.

The increase demonstrated in the diastolic diameter of the fetal descending aorta could have resulted from a peripheral fetal vasoconstriction in combination with an increase in the afterload found after smoking in humans (13). An increase in cardiac output is seen in animals after catecholamine infusion (10,14) and also in humans after smoking (13) together with an increase in the velocity of myocardial contraction and contractility force (13). These effects may have caused the 20.2% increase in the aortic blood velocity found in this study and, together with the change in the aortic diastolic diameter, could have been responsible for the 29.6% increase in the aortic blood flow. The maximum velocity of the aortic blood flow is considered to be a reflection of stroke volume (3). Therefore the present finding of an increase in the maximum peak blood velocity suggests an increased stroke volume also in the human fetus after maternal smoking.

The umbilical blood flow in the fetal lamb was found to correlate positively with the fetal heart rate and arterial blood pressure (15). In this investigation, we found that smoking was followed by a significant increase in the umbilical vein blood flow, by 38.5% of the control values. Atropine administration to chronically catheterized fetal lambs increased the fetal heart rate and the umbilical venous blood flow without affecting the umbilical blood pressure (1), which suggests that the autonomic nervous system only minimally affects the basal umbilical venous flow. The unchanged velocity of the blood in the umbilical circulation, together with the increase in the umbilical blood flow beginning later than the increase in the aortic

blood flow, as found in this investigation points in the same direction.

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